

Functional Outcome of Elderly Survivors of Ischemic Stroke: A Retrospective Study Comparing Non-Hypercholesterolemic and Hypercholesterolemic Patients

Eliyahu Hayim Mizrahi MD MHA^{1,2}, Anna Waitzman MD¹, Marina Arad MD^{1,2} and Abraham Adunsky MD^{1,2}

¹Department of Geriatric Medicine and Rehabilitation, Sheba Medical Center, Tel Hashomer, Israel

²Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: **Background:** Total cholesterol is significantly associated with increased risk of ischemic stroke. Patients with ischemic stroke and high cholesterol levels may show better functional outcome after rehabilitation.

Objectives: To study the possible interrelations between hypercholesterolemia and functional outcome in elderly survivors of ischemic stroke.

Methods: We conducted a retrospective chart review study of consecutive patients (age ≥ 60 years) with acute stroke admitted to a geriatric rehabilitation ward in a university-affiliated hospital. The presence or absence of hypercholesterolemia was based on registry data positive for hypercholesterolemia, defined as total cholesterol ≥ 200 mg/dl (5.17 mmol/L). Functional outcome of patients with hypercholesterolemia (Hchol) and without (NHchol) was assessed by the Functional Independence Measurement scale (FIM™) at admission and discharge. Data were analyzed by *t*-test and chi-square test, as well as linear regression analysis.

Results: The complete data for 551 patients (age range 60–96 years) were available for final analysis; 26.7% were diagnosed as having hypercholesterolemia. Admission total FIM scores were significantly higher in patients with Hchol (72.1 ± 24.8) compared with NHchol patients (62.2 ± 24.7) ($P < 0.001$). A similar difference was found at discharge (Hchol 90.8 ± 27.9 vs. NHchol 79.7 ± 29.2 , $P < 0.001$). However, total FIM change upon discharge was similar in both groups (18.7 ± 13.7 vs. 17.6 ± 13.7 , $P = 0.4$). Regression analyses showed that high Mini Mental State Examination scores ($\beta = 0.13$, $P = 0.01$) and younger age ($\beta = -0.12$, $P = 0.02$) were associated with higher total FIM change scores upon discharge. Total cholesterol was not associated with better total FIM change on discharge ($\beta = -0.012$, $P = 0.82$).

Conclusions: Elderly survivors of stroke with Hchol who were admitted for rehabilitation showed higher admission and discharge FIM scores but similar functional FIM gains as compared to NHchol patients. High cholesterol levels may be useful in identifying older individuals with a better rehabilitation potential.

KEY WORDS: cholesterol, elderly, functional outcome, ischemic stroke, rehabilitation

A nationwide Israeli study conducted in 2004 documented the high burden associated with acute stroke [1] and estimated that about 13,000 people are admitted annually due to acute stroke. A 5-year survey of survival after stroke in Israel did not find any association between cardiovascular risk factors and mortality [2], yet high total cholesterol levels were shown to increase the relative risk of mortality from ischemic stroke by 11% in an Israeli male population [3].

The interrelations between stroke and cholesterol are complex and contain several paradoxes. In subjects older than 75 years, being in the lowest quartile of cholesterol level is associated with increased mortality [4], and levels below 189 mg/dl have been suggested as an early sign of unidentified comorbidity or of a rapid functional decline [5]. In contrast to the well-established association of various lipids levels and coronary heart disease [6], the epidemiological evidence connecting lipid levels with increased risk of ischemic stroke is less clear. Some studies found increased risk of ischemic stroke associated with increased total cholesterol levels [7], while others failed to show a clear association [8]. Another intriguing aspect of the relationship between total cholesterol and stroke is the possible prognostic value of total cholesterol levels in the period following acute ischemic stroke. To date, only a few studies on the effect of total cholesterol on survival after stroke have been published and they yielded different results. Censori et al. [9] showed that total cholesterol levels were not associated with short-term outcome in terms of disability and death, while Dyker and colleagues [10] reported an inverse association between lower total cholesterol levels and 3-month, but not 30-day, total mortality. More recently it has been shown

FIM = Functional Independence Measurement
Hchol = hypercholesterolemia
NHchol = non-hypercholesterolemia

that high total cholesterol levels were associated with better prognosis in the early stage (first month) following ischemic stroke [11]. A 10-year follow-up study of ischemic stroke concluded that higher total cholesterol levels were associated with less severe stroke as well as with reduced mortality rates [12]. Moreover, compared to patients with normal cholesterol levels, those with high cholesterol levels in the first month following ischemic stroke had a 2.2-fold lower risk of death [11]. This last study evaluated the functional outcome of stroke patients with hypercholesterolemia and suggested that higher levels of cholesterol are associated with a better outcome in the early phase after ischemic stroke. However, that study comprised relatively young stroke patients (mean age < 63), reported function only one month following stroke, was not conducted in a rehabilitation setting and did not evaluate rehabilitation outcome in terms of a standardized functional score system. Therefore, the purpose of the present study was to investigate the possible relationship of hypercholesterolemia and functional outcome as evaluated by the Functional Independence Measure, controlling for the presence of some prevalent comorbidities characteristic of these patients. In accordance with previous studies, we hypothesized that ischemic stroke patients with high total cholesterol levels might show a better functional outcome as compared with non-hypercholesterolemic patients.

PATIENTS AND METHODS

The study included 603 consecutive patients with acute stroke. Patients were admitted to the department of geriatric rehabilitation over a 48-month period (1 January 2004 – 31 December 2007) after a short stay in the departments of internal medicine or neurology. Primary inclusion criteria included stable medical status, enabling active rehabilitation treatment. Patients aged 60 years or older, with length of stay in the rehabilitation ward of less than 7 days (assuming that the extent of rehabilitation in such a short period is limited), residual brain damage due to infection, trauma or surgery, and patients with space-occupying lesions or hemorrhagic stroke were excluded. Deceased patients (n=23) were also excluded due to incomplete data (e.g., FIM on discharge). Stroke was diagnosed on the basis of clinical presentation of acute onset of focal neurological signs. Computed tomography or magnetic resonance imaging scans were performed in all cases to confirm the presence and nature of ischemic stroke. The presence or absence of hypercholesterolemia (total cholesterol \geq 200 mg/dl, 5.17 mmol/L) was based on registry data positive for hypercholesterolemia (ICD 9 code 272.0). This registry data-recording system did not allow analysis of cholesterol levels as continuous variables.

The presence of other relevant risk factors such as arterial hypertension, ischemic heart disease (manifested as stable or unstable anginal syndrome), atrial fibrillation, previous

stroke and diabetes mellitus were established by the medical history obtained during an interview of patients and/or caregivers, and a complete physical examination, as well as by the use of medical file codes from the International Coding of Diseases, 9th Revision (ICD-9).

SETTING AND PROCEDURE

In this retrospective chart review study we evaluated the possible associations between cholesterol status in stroke patients and their functional outcomes at discharge. The geriatric rehabilitation department is a 36-bed unit. This ward uses an interdisciplinary team approach, whereby medical personnel (physicians; nurses; physical, occupational and speech therapists; social workers; and psychologists) meet twice a week to evaluate the status of each patient. During these meetings, treatment plans are established and monitored. The patients undergo, on average, 6 hours of physical therapy and 6 hours of occupational therapy a week, and additional rehabilitation treatment as needed. Each patient was evaluated twice (on admission and discharge) for level of disability, by the FIM scale [13]. This tool is widely used to rate patients' performances on 18 activities of daily living. Total FIM scores range between 18 (reflecting complete dependence in all functional skills) and 126 (reflecting complete independence in all functional skills). In addition we calculated motor FIM, which consists of the 13 motor items of this scale (without the cognitive FIM items). Motor FIM score therefore ranges between 13 (minimum) and 91 (maximum) points. We also calculated FIM gain (total and motor) and daily FIM gain (total and motor). All patients were also evaluated for their cognitive level by the Mini Mental State Examination [14].

DATA ANALYSIS

Comparisons between patients with and without hypercholesterolemia were performed for a list of clinical and functional measures using *t*-tests for continuous variables and chi-square tests for dichotomous variables. Multiple linear regression analysis was performed to assess the independent associations of serum cholesterol status and demographic and clinical characteristics with total functional outcome by motor, total and FIM gain scores at discharge and with change in total functional outcome between admission and discharge. A *P* value \leq 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS system for Windows, version 10.0.1.

RESULTS

The data of 603 consecutive patients (age range 60–96 years) admitted with acute stroke were available. Fifty-two patients were excluded due to age < 60 years, non-ischemic nature of stroke, ward stay < 7 days, or death. The remaining 551 patients with a recent acute ischemic stroke were included in the final analysis. The clinicodemographic characteristics of these

Table 1. Clinical and cognitive characteristics of patients

Variables	All patients	NHchol	Hchol	P value
Sample size, n (%)	551	404(73.3)	147(26.7)	
Age (yrs, mean ± SD)	74.6 ± 9.2	75.5 ± 9.3	72.1 ± 8.6	< 0.001*
Gender (male %)	58.40	60.90	51.70	0.05†
Length of stay (days, mean ± SD)	46.6 ± 26.8	47.6 ± 27.1	43.8 ± 25.8	0.1*
Diabetes (%)	38.80	34.90	49.70	0.002†
Hypertension (%)	67	62.40	79.60	< 0.001†
Ischemic heart disease (%)	30.90	31.20	29.90	0.7†
Atrial fibrillation (%)	16.20	18.10	10.90	0.04†
Previous stroke (%)	19.80	20.80	17	0.3†
MMSE score (mean ± SD)	22.4 ± 5.4	22.1 ± 5.6	23.0 ± 4.9	0.1*

*Based on two-tailed Student's t-test

†Based on chi-square test

NHchol = non-hypercholesterolemia, Hchol = hypercholesterolemia, MMSE = Mini Mental State Examination

Table 2. Functional characteristics of patients by total cholesterol

Variables	NHchol	Hchol	P value
Admission total FIM (mean ± SD)	62.2 ± 24.7	72.1 ± 24.8	< 0.001
Discharge total FIM (mean ± SD)	79.7 ± 29.2	90.8 ± 27.9	< 0.001
Change in total FIM (mean ± SD)	17.6 ± 13.7	18.7 ± 13.7	0.4
Admission motor FIM (mean ± SD)	39.9 ± 18.4	46.8 ± 19.0	< 0.001
Discharge motor FIM (mean ± SD)	55.9 ± 22.2	64.2 ± 21.9	< 0.001
Change in motor FIM (mean ± SD)	15.9±11.9	17.4±12.4	0.1

*Based on two-tailed Student's t-test

NHchol = non-hypercholesterolemia, Hchol = hypercholesterolemia, FIM = functional independence measurement

patients are shown in Table 1. Mean age was 74.6 ± 9.2 years and most (58.4%) of the patients were male. Only 26.7% of the patients were hypercholesterolemic. There was a statistically significant difference between patients with Hchol (n=147) and the remaining patients (n=404) by age ($P < 0.001$), male gender ($P = 0.05$), diabetes mellitus ($P = 0.002$), arterial hypertension ($P < 0.001$) and atrial fibrillation ($P = 0.04$) [Table 1].

Patients with Hchol had statistically significant higher total FIM scores at admission ($P < 0.001$) and discharge ($P < 0.001$) compared with NHchol. These patients also had statistically significant higher motor FIM scores on admission ($P < 0.001$) and discharge ($P < 0.001$) [Table 2]. However, there was no statistically significant difference between the NHchol and the Hchol group in total and motor FIM change [Table 2]. We also performed multiple linear regression analysis to test the net effect of predictors on total FIM and on change in total FIM at hospital discharge. The results show that a higher MMSE

Table 3. Analysis of factors predicting total FIM at discharge

Independent predictors	Beta	P value*
Total cholesterol	0.11	0.02
Age	-0.17	< 0.001
Gender	-0.006	0.89
Hypertension	0.054	0.23
Diabetes	-0.027	0.56
Atrial fibrillation	-0.02	0.75
Ischemic heart disease	0.027	0.55
Parkinson 's disease	-0.061	0.18
Previous stroke	0.022	0.62
MMSE score	0.41	< 0.001

*Based on multiple regression analysis

MMSE = Mini Mental State Examination

Table 4. Analysis of factors predicting total FIM change at discharge

Independent predictors	Beta	P value*
Total cholesterol	-0.012	0.82
Age	-0.12	0.02
Gender	0.064	0.22
Hypertension	0.038	0.46
Diabetes	-0.052	0.31
Atrial fibrillation	-0.058	0.26
Ischemic heart disease	0.031	0.54
Parkinson 's disease	-0.09	0.078
Previous stroke	-0.081	0.12
MMSE score	0.13	0.013

*Based on multiple regression analysis

MMSE = Mini Mental State Examination

score ($\beta = 0.41, P < 0.001$) is a significantly predictive factor of higher total FIM scores at discharge, while high total cholesterol predicts a higher total FIM score at discharge ($\beta = 0.11, P = 0.02$) [Table 3].

As shown in Table 4, total FIM change was independently, and inversely, associated with age ($\beta = -0.12, P = 0.02$), while higher MMSE score ($\beta = 0.13, P < 0.013$) is a significantly predictive factor of higher total FIM change at discharge. Total cholesterol did not predict a higher FIM change at discharge ($\beta = -0.012, P = 0.82$).

DISCUSSION

The main finding of this study was that the overall functional outcome of elderly stroke survivors was better for hypercholesterolemic patients, compared with those who were not. Total and motor absolute scores at admission and discharge were higher in such patients. However, both motor and total

MMSE = Mini Mental State Examination

FIM gains were similar in the two groups. This association was independent of a large number of prognostic factors but remained dependent upon cognitive state and age, known to play a major prognostic role in stroke rehabilitation [15]. Overall, the present study of a sample of elderly patients extends the results of a previous study [11] conducted in a younger stroke population that suggested an association of high cholesterol with a better functional outcome.

There are a few possible explanations for an ameliorating effect of high total cholesterol on functional outcome. These may include the fact that high cholesterol is a marker of a better nutritional and general health condition [16] contributing to improved outcome. This is in accordance with previous studies on the decrease of total cholesterol levels during the acute phase of stroke [17,18], hence, reflecting stroke severity. We therefore suggest that high cholesterol in these patients, at least during their stay in an acute inpatient rehabilitation setting, should be considered a favorable positive biological marker. Another explanation for cholesterol's ameliorating effect is the protective effect exerted by cholesterol on cell membrane fluidity [19], the responsiveness to vasodilator stimuli [20], and the blunting of unfavorable effects of oxidative stress on cerebral tissue [21]. In addition, our patients with normal cholesterol were older (75.5 ± 9.3 vs. 72.1 ± 8.6 years) and were less likely to suffer from diabetes and hypertension, but more likely to have atrial fibrillation or a previous stroke. This suggests that normocholesterolemic elderly patients represent a more vulnerable population, and reflects the fact that in patients over age 70 the levels of total cholesterol tend to decrease [22], which is perhaps one of several physiological derangements. The results may raise the issue of secondary stroke prevention in the elderly by use of cholesterol-lowering agents. While it is clear that we need to reduce the risk of stroke recurrence by all available means, there is still concern regarding the effectiveness of such treatment [23] and a lack of evidence-based studies in this population, so that current recommendations and guidelines applying to younger patients who have had a stroke [24] are still questionable. Our results may hint that cholesterol-lowering treatment should be less aggressively instituted, if at all, in older stroke patients. However, due to the limitations of these preliminary results, caution should be applied when considering the option of withdrawing cholesterol-lowering treatment in this high-risk population. Interestingly, there was a higher proportion of atrial fibrillation in patients without hypercholesterolemia. A similar cholesterol and triglycerides paradox has been shown in patients with paroxysmal atrial fibrillation, and it has been suggested that low hypolipoproteinemia may affect atrial vulnerability and cause atrial fibrillation [25].

Possible limitations of our study are its retrospective nature and design, and the fact that it included only the survivors of acute ischemic stroke, which does not allow for the establishment of a cause-effect relationship between hypercholesterolemia and functional outcome. The cutoff line

of 200 mg/dl for total cholesterol may be argued, although it is commonly used in clinical practice. Using cholesterol as a dichotomous variable makes it impossible to rule out that some patients classified as "normal cholesterol" may have very low levels associated with poor nutrition. In addition, despite a careful adjustment made for important confounders, still others could have been considered. In particular, the data did not allow analysis of cholesterol levels (or its sub-fractions) as continuous variables, and did not consider pre-stroke cholesterol status or a possible change in cholesterol over time. We also did not incorporate any data of cholesterol-lowering medications. Moreover, generalizability to other populations rather than elderly stroke patients may be limited. A validation study of registry data, including accuracy of source documents and the level of skill and care applied in abstracting data, was not performed. Finally, longitudinal follow-up data would contribute to a better understanding of the interrelations between cholesterol and function in later stages. Despite these limitations, the present study is advantageous in the sense that it comprised a large sample of patients, all of whom underwent a similar rehabilitation program in a dedicated ward designed to treat elderly stroke patients, thus decreasing any degree of selection bias and increasing the validity of the study.

We conclude that functional outcome in elderly survivors of acute ischemic stroke undergoing rehabilitation is slightly more favorable in hypercholesterolemic patients, independently of a large number of prognostic factors. High cholesterol levels might also be useful in identifying older individuals with a better rehabilitation potential. Further studies are needed to confirm our observation.

Corresponding author:

Dr. E.H. Mizrahi

Dept. of Geriatric Medicine and Rehabilitation, Sheba Medical Center, Tel Hashomer 52621, Israel

Phone: (972-3) 530-3398

Fax: (972-3) 530-3399

email: exm42@sheba.health.gov.il

References

1. Tanne D, Goldbourt U, Koton S, et al. A national survey of acute cerebrovascular disease in Israel. Burden, management, outcome and adherence to guidelines. *IMAJ Isr Med Assoc J* 2006; 8: 3-7.
2. Bentur N, Resnitzky S. Five year survival after stroke, and related prognostic factors in Israel. *IMAJ Isr Med Assoc J* 2009; 11: 411-15.
3. Tanne D, Yaari S, Goldbourt U. High-density lipoprotein cholesterol and risk of ischemic stroke mortality. A 21-year follow-up of 8586 men from the Israeli Ischemic Heart Disease Study. *Stroke* 1997; 28: 83-7.
4. Spada RS, Toscano G, Cosentino FI, et al. Low total cholesterol predicts mortality in the nondemented oldest old. *Arch Gerontol Geriatr* 2007; 44 (Suppl 1): 381-4.
5. Petermans J, Laperche J, Scheen AJ. Do statins have a place for cardiovascular prevention in elderly people? *Rev Med Liege* 2006; 61: 386-93.
6. Shay I, Rimm EB, Hankinson SE, et al. Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women: potential implications for clinical guidelines. *Circulation* 2004; 110: 2824-30.

7. Kurth T, Everett BM, Buring JE, Kase CS, Ridker PM, Gaziano JM. Lipid levels and the risk of ischemic stroke in women. *Neurology* 2007; 68: 556-62.
8. Bowman TS, Sesso HD, Ma J, et al. Cholesterol and the risk of ischemic stroke. *Stroke* 2003; 34: 2930-4.
9. Censori B, Camerlingo M, Casto L, et al. Prognostic factors in first-ever stroke in the carotid artery territory seen within 6 hours after onset. *Stroke* 1993; 24: 532-5.
10. Dyker AG, Weir CJ, Lees KR. Influence of cholesterol on survival after stroke: retrospective study. *BMJ* 1997; 314: 1584-8.
11. Vauthey C, de Freitas GR, van Melle G, Devuyt G, Bogousslavsky J. Better outcome after stroke with higher serum cholesterol levels. *Neurology* 2000; 54: 1944-9.
12. Olsen TS, Christensen RH, Kammersgaard LP, Andersen KK. Higher total serum cholesterol levels are associated with less severe strokes and lower all-cause mortality: ten-year follow-up of ischemic strokes in the Copenhagen Stroke Study. *Stroke* 2007; 38: 2646-51.
13. Linacre JM, Heinemann AW, Wright BD, Granger CV, Hamilton BB. The structure and stability of the Functional Independence Measure. *Arch Phys Med Rehabil* 1994; 75: 127-32.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State," a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189-98.
15. Hinkle JL. Variables explaining functional recovery following motor stroke. *J Neurosci Nurs* 2006; 38: 6-12.
16. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet* 2001; 358: 351-5.
17. Woo J, Lam CWK, Wong HY, Teoh R, Nicholls MG. Acute and long-term changes in serum lipids after acute stroke. *Stroke* 1990; 21: 1407-11.
18. Butterworth RJ, Marshall WJ, Bath PMW. Changes in serum lipid measurements following acute ischemic stroke. *Cerebrovasc Dis* 1997; 7: 10-13.
19. Joseph JA, Villalobos-Molinas R, Denisova NA, Erat S, Strain J. Cholesterol: a two-edged sword in brain aging. *Free Radic Biol Med* 1997; 22: 455-62.
20. De Roos NM, Bots ML, Siebelink E, Schouten E, Katan MB. Flow-mediated vasodilatation is not impaired when HDL-cholesterol is lowered by substituting carbohydrates for monounsaturated fat. *Br J Nutr* 2001; 86: 181-8.
21. Vatassery GT, Smith WE, Quach HT, Lai CK. In vitro oxidation of vitamin E, vitamin C, thiols, and cholesterol in rat brain mitochondria incubated with free radicals. *Neurochem Int* 1995; 26: 527-35.
22. Brescianini S, Maggi S, Farchi G, et al; ILSA Group. Low total cholesterol and increased risk of dying: are low levels clinical warning signs in the elderly? Results from the Italian Longitudinal Study on Aging. *J Am Geriatr Soc* 2003; 51: 991-6.
23. Simpson CR, Wilson C, Hannaford PC, Williams D. Evidence for age and sex differences in the secondary prevention of stroke in Scottish primary care. *Stroke* 2005; 36: 1771-5.
24. Stroke Council, American Heart Association; American Stroke Association. Statins after ischemic stroke and transient ischemic attack: an advisory statement from the Stroke Council, American Heart Association and American Stroke Association. *Stroke* 2004; 35: 1023.
25. Annoura M, Ogawa M, Kumagai K, Zhang B, Saku K, Arakawa K. Cholesterol paradox in patients with paroxysmal atrial fibrillation. *Cardiology* 1999; 92: 21-7.

Capsule

Axons severed by lasers in the nematode *Caenorhabditis elegans* can fuse and reestablish function

Peripheral nerves show some ability to regenerate after damage, but it is not an easy process. When an axon is severed, the neuronal cell body must convert the remaining axon stump into a developing axon with a growth cone. Then the axon must find its way past the damaged region and on to its original target, along the way contending with disrupted tissues, inhibitory signals, and an absence of the developmental signals that built the connection in the first place. In crayfish, earthworm and leech, the tip of a severed axon can actually fuse with the distal remainder of the axon, leapfrogging over regeneration hurdles. Neumann et al. show that axons severed by lasers in the nematode *Caenorhabditis*

elegans can fuse and reestablish function. As the axon stumps regenerated, they often came into contact with the distal remainder, which could then be reincorporated into neuronal function. The membranes fused and cytoplasmic movements connected pre- and post-injury portions of the axon. Without such contact, the distal remainder degenerated and disappeared. When more than one axon was severed, the axons usually found the correct partners. The molecular cues that help a growth cone identify its fusion partner remain to be elucidated.

Dev Dyn 2011; 240: 10.1002/dvdy.22606

Eitan Israeli

Capsule

Cardiac myosin activation as a potential therapeutic approach for systolic heart failure

Decreased cardiac contractility is a central feature of systolic heart failure. Existing drugs increase cardiac contractility indirectly through signaling cascades but are limited by their mechanism-related adverse effects. To avoid these limitations, we previously developed omecamtiv mecarbil, a small-molecule, direct activator of cardiac myosin. Malik et al. show that it binds to the myosin catalytic domain and operates by an allosteric mechanism to increase the transition rate of myosin into the strongly actin-bound force-generating

state. Paradoxically, it inhibits adenosine 5'-triphosphate turnover in the absence of actin, which suggests that it stabilizes an actin-bound conformation of myosin. In animal models, omecamtiv mecarbil increases cardiac function by increasing the duration of ejection without changing the rates of contraction. Cardiac myosin activation may provide a new therapeutic approach for systolic heart failure.

Science 2011; 331: 1439

Eitan Israeli

Current Changes in the Management and Outcome of Patients with Curable Colorectal Cancer

Refael Itah MD¹, Ron Greenberg MD¹, Nachum Werbin MD¹, Einat Sacham-Shmueli MD², Roy Inbar MD¹ and Shmuel Avital MD¹

Departments of ¹Surgery A and ²Oncology, Tel Aviv Sourasky Medical Center affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: **Background:** Major changes in the evaluation and treatment of curable colorectal cancer (CRC) have emerged in the last two decades. These changes have led to better patient outcome over time.

Objectives: To evaluate the impact of these changes as reflected in the difference in long-term outcome of a consecutive group of recently laparoscopically operated curable CRC patients and a consecutive group of patients operated 20 years earlier in the same department.

Methods: Data of the new group were taken from our prospectively collected data of patients who underwent elective laparoscopic surgery for CRC in recent years. Data regarding patients operated on 20 years ago were retrieved from previous prospectively collected data on the long-term survival of CRC patients operated in the same department.

Results: The recently operated group comprised 203 patients and the previous group 199 patients. Perioperative mortality was 0.5% in the new group versus 1.5% in the old group (not significant). There were more early-stage and more proximal tumors in the recently operated group. A Kaplan-Meier 5-year survival analysis revealed no difference between stage I patients of the two groups. However, there was a significant increase in 5-year survival in the new group for stage II (85% vs. 63%, $P = 0.004$) and for stage III patients (57% vs. 39%, $P = 0.01$). This trend was maintained after removing the rectal cancer patients from the calculated data.

Conclusions: We have demonstrated improved survival for stage II and III CRC patients over a 20-year period in the same medical center. This change most likely reflects advances both in imaging techniques leading to more accurate staging and in adjuvant treatments.

IMAJ 2011; 13: 300–303

KEY WORDS: colorectal surgery, colorectal cancer, survival

related to the stage at diagnosis. Treatment for curable CRC consists of adequate oncological surgery and adjuvant treatment when indicated.

The approach to colorectal cancer has changed over the last decade in several aspects. More emphasis is given to screening programs [2] since they lead to early detection and the resultant increased survival [3]. Operative procedures have become less invasive and well tolerated by patients due to the increased use of laparoscopy [4]. This process was somewhat slow to evolve owing to early concerns related to oncological safety [5] that were later resolved [6–8]. Since the early 1990s adjuvant treatment after surgery became the standard of care in node-positive patients and in selected stage II patients. This together with new potent chemotherapeutic drugs that have emerged in recent years have led to a substantial increase in the overall survival of advanced CRC patients [9].

The purpose of the present study was to evaluate how all the abovementioned changes were reflected in the outcome of patients with curable colorectal cancer operated in the same medical center over a long period. This was done by comparing patient and tumor characteristics and long-term survival between patients who were operated almost two decades ago [10] and a consecutive group of patients who recently underwent laparoscopic surgery by a dedicated surgical team from the same department.

PATIENTS AND METHODS

The 'old' group of patients comprised consecutive patients who were electively operated for curable colorectal cancer in our department during the period 1984–1987. The 'new' group of patients comprised consecutive elective patients operated laparoscopically during the period September 2003 to December 2009 by a dedicated laparoscopic team from the same department.

Data for the old group were extracted from an existing database on patients' long-term survival that we used in a previous study published in 1997 [10]. This group of patients included all consecutive patients electively operated during this period. Data for the new group were retrieved from our prospectively collected data on all patients undergoing laparoscopic colorectal surgery. Almost all the procedures were

Carcinoma of the colon and rectum is the third most common cancer in North America, with an incidence of 147,000 new cases and 50,000 cancer-related deaths per year [1]. The prognosis of patients with colorectal cancer is

CRC = colorectal cancer

performed or directed by one of two surgeons dedicated to this approach. Long-term data in this group were collected from our outpatient clinic data files and personal contact when necessary. The data collection was approved by the institutional review board.

STATISTICS

Statistical analysis was performed using the chi-square test, *t*-test, Mann-Whitney non-parametric test, and long rank test for Kaplan-Meier survival curves. *P* value less than 0.05 was considered significant.

RESULTS

THE OLD GROUP

This group consisted of 199 patients, for whom follow-up was available for 184 (92.4%). In all of them follow-up time was > 5 years. None of these patients received adjuvant chemotherapy, while 14 rectal cancer patients received adjuvant radiotherapy.

THE NEW GROUP

This group consisted of 203 patients, for whom follow-up was available for 202 (99.5%). Fourteen percent of the patients had completed at least 5 years of follow-up since their operation. Mean follow-up time in this group was 30 months. None of the stage I patients received adjuvant treatment while 33% and 75% of stage II and III patients respectively received some form of adjuvant treatment.

GROUP COMPARISON

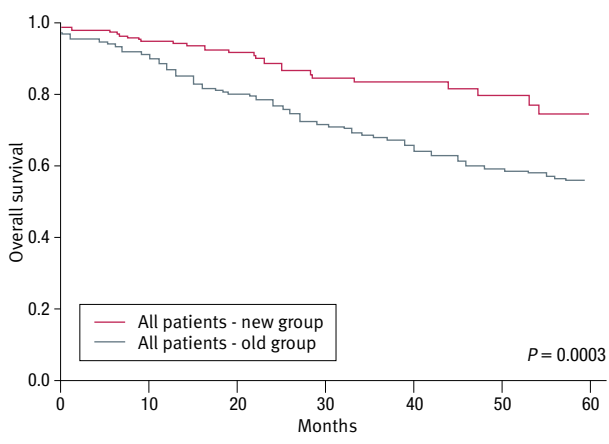
Mean age, the ratio between males and females, and operative mortality did not differ between the two groups. Stage distribution revealed more early stages in the new group. Also found were more right-sided tumors and fewer rectal tumors in the new group [Table 1].

Table 1. Demographic data, mortality, stage distribution and tumor location

	Old group N=199	New group N=203	<i>P</i> value
Mean age (yrs)	70.2 ± 12.4	69.9 ± 11.1	NS
M/F ratio	1.16	0.83	NS
Peri-operative mortality	3 (1.5%)	1 (0.5%)	NS
Stage			
I	28 (14%)	66 (32.3%)	< 0.01
II	108 (54.3%)	72 (35.3%)	0.02
III	63 (31.6%)	65 (31.9%)	NS
Location			
Rt. colon	54 (27%)	94 (46.3%)	0.007
Lt. colon/sigma	83 (42%)	72 (35.4%)	NS
Rectum	56 (28%)	33 (16.2%)	0.02

NS = not significant

Figure 1. Kaplan-Meier 5-year overall survival analysis for all patients: new group versus old group (75% vs. 57%, *P* = 0.003)



LONG-TERM OVERALL SURVIVAL

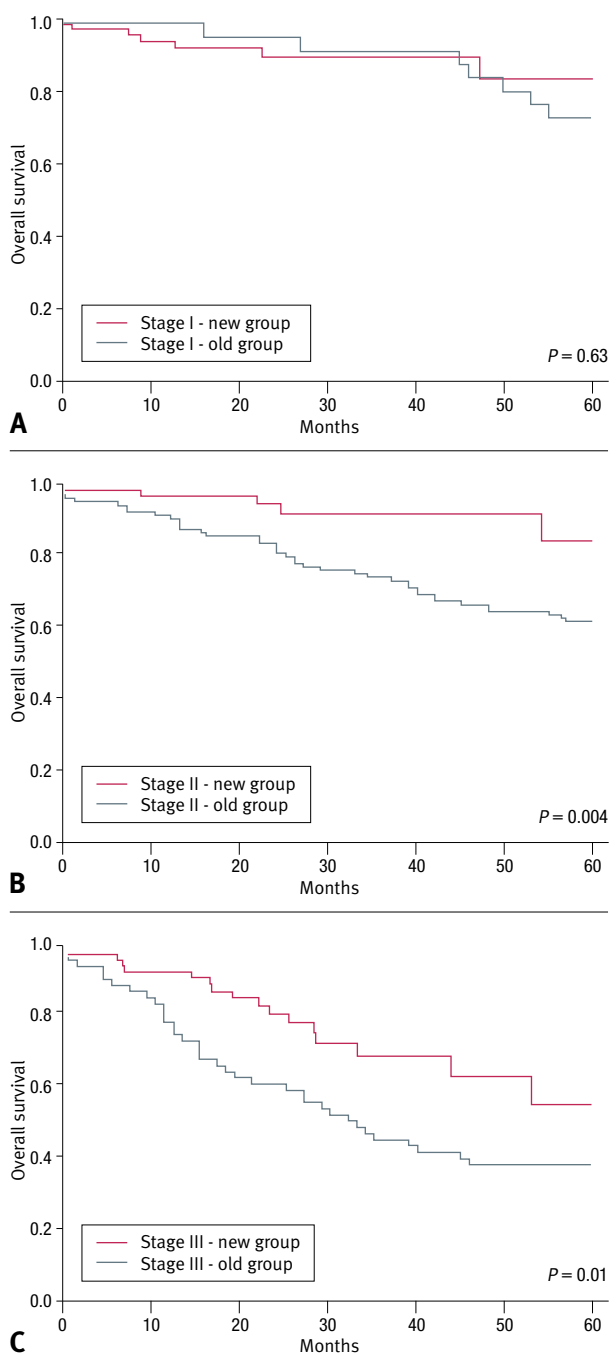
Survival comparison between the two groups demonstrated increased overall survival in the new group (75% versus 57% 5-year survival, *P* = 0.0003) [Figure I]. Survival comparison according to disease stage revealed a similar 5-year overall survival in stage I. However, an increased overall survival in stage II (85% vs. 63% 5, *P* = 0.004) and in stage III (57% vs. 39%, *P* = 0.01) was demonstrated in the new group [Figure 2]. This trend was maintained also after removing the rectal cancer patients from the calculated data (84% vs. 62% 5-year survival in stage II patients, *P* = 0.01 and 64% vs. 41% in stage III patients, *P* = 0.03).

DISCUSSION

Over the past 20 years the approach to and treatment of colorectal cancer have changed in many aspects. Implementation of screening programs, the use of less invasive surgical methods (i.e., laparoscopy), and the concept and development of better adjuvant treatments have modified both our treatment approach and patient outcome. These changes are reflected in the present study, which demonstrates the different outcome of operated patients with CRC over a 20-year period in the same department.

Comparing the two groups of patients in terms of stage and location of the cancer revealed an earlier stage and more right-sided tumors in the new laparoscopic group. The prevalence of an earlier-stage cancer in the new group may reflect an overall change over the last decade due to more public awareness and the availability of screening programs that result in early detection of colorectal cancer. Gross et al. [11] demonstrated a significant increase in probability of being diagnosed at an early stage in a population that was reimbursed for screening colonoscopy since 1998 compared to before. Fazio and col-

Figure 2. Kaplan-Meier 5-year overall survival analysis: new group versus old group. **[A]** Stage I patients (84% vs. 73%, not significant). **[B]** Stage II patients (75% vs. 57%, $P = 0.003$). **[C]** Stage III patients.



laborators [3] reported the same trend for public education and screening programs. The change in tumor location in our study may reflect a universal process of rightward shift over time, with more proximal tumors diagnosed in recent decades [12]. This

phenomenon may be attributed to better screening of the proximal colon, increased routine performance of full colonoscopy, and general dietary changes over the past few decades [13].

Our study included a consecutive group of patients who were operated laparoscopically by a dedicated laparoscopic team. This fact may have produced some bias with regard to comparison of the group's characteristics since this group did not include patients who underwent open procedures for any reason (i.e., team decision or operation by non-laparoscopic surgeon). Obviously, the traditional open surgical approach was used in the old group of patients as laparoscopy was not a possible surgical approach 20 years ago.

The difference in tumor location may also be attributed to a change in referral patterns over 20 years. It may be that the laparoscopic approach was applied to more patients with right colonic tumors because rectal cancer patients were referred or chose other dedicated colorectal surgeons who did not employ laparoscopic surgery. However, we have no way of evaluating the impact of the change in referral patterns on the case-mix of our new group of patients. Nevertheless, we can presume that the surgical approach (i.e., laparoscopy versus open) had no impact on the difference between the long-term outcome, since it was repeatedly confirmed that laparoscopy has postoperative benefits but does not change patient survival compared to the open approach [6,7]. Unfortunately, in this study we could not compare postoperative recovery parameters between the two groups as these data were not available for the old group.

A change in surgical approach that could have an impact on survival is the introduction and implementation of the TME technique (total mesorectal excision) in recent years for rectal cancer patients. The TME approach demonstrated a lower local recurrence rate [14] and improved overall survival [15]. Unfortunately, in our study we could not assess the rectal cancer patients separately because the numbers were too small for significant survival analysis. However, evaluation of the colon cancer-only patients in our series revealed the same trend of better survival in the new group. This underlines the fact that the survival improvement is due to several factors, though location (colon versus rectum) might be one of them.

Data regarding quality measures for oncological resection as reflected in resection margins and the number of harvested nodes were available for the present laparoscopic group. The surgical margins and the mean number of harvested lymph nodes in this group concur with the standards of adequate oncological resection [16-18]. These data were not available for the old patient group; however, we can presume that the quality of surgery was not different 20 years ago as the same surgical oncology principles existed then and now.

This study demonstrated no change in long-term outcome for stage I CRC patients over the years. This result is reason-

TME = total mesorectal excision

able since the prognosis of stage I patients following adequate surgery is very good, with no need for further treatment apart from close follow-up. However, we have shown a significant improvement in survival for stage II and III CRC patients. We believe that the survival improvement can be attributed to the substantial advance in adjuvant therapy and better staging due to improved imaging techniques. The introduction of the 5 FU/leukoverin adjuvant treatment as the standard of care for stage III patients and selected stage II patients and the recent addition of oxaliplatin has substantially increased patient survival [19]. It is important to note that adjuvant chemotherapy was not the standard of care in the years 1984–1987 in our department.

In addition to the improvement in adjuvant treatment, the improved imaging techniques have probably contributed to more accurate staging. The improved sensitivity of computed tomography and the development of the positron emission tomography scan may have enhanced the accuracy of staging evaluation in discovering small metastases that could not be identified 20 years ago. This may lead to the exclusion of stage IV patients from our present patients who may not have been excluded 20 years ago and were likely considered to be in a lower stage.

The surgical principles of colon cancer resection that are currently practiced were the same as those followed when our old group was operated and even long before [20]. However, the recent focus on the number of retrieved lymph nodes may influence the pathologist as well as the surgeon to perform a more extensive dissection. Recent studies have emphasized the importance of the number of retrieved and examined nodes in the resected specimen. Increased lymph node evaluation may lead to better staging and may have an impact on long-term survival [21]. This perception did not exist 20 years ago and thus it is possible that some patients who were considered stage II in our old group were understaged due to less accurate pathological evaluation or less extensive surgery leading to a worse long-term survival in this group. Yet, as mentioned earlier, we do not have the data on the number of evaluated nodes in our old patient group to support this assumption.

General improvement in survival of colorectal cancer patients over the last decade was demonstrated in several studies using databases of cancer registries [22,23]. The major reason for this improvement is the enhanced prognosis of patients with regional tumor spread undergoing curative surgery [22]. Many of the reasons for this change that were suggested by others [23] were demonstrated and discussed in our study.

In conclusion, we have demonstrated improved overall survival for stage II and III CRC patients undergoing curative surgery over a 20-year period. This study is unique in that it compares two groups of patients operated by teams from the same department over a long period. Our results are in accordance with epidemiological reports from large database registries. Today, a colorectal cancer patient has a higher probability of being diagnosed at an early stage, having

a proximal tumor, undergoing laparoscopic surgery, receiving adjuvant treatment when indicated, and living longer than was possible two decades ago.

Corresponding author:

Dr. S. Avital

Dept. of Surgery A, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel

Phone: (972-3) 694-7289, **Fax:** (972-3) 697-4820

email: avitalshmuel@gmail.com

References

- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; 59 (4): 225-49.
- Lachter J, Leska-Aharoni T, Warum D, Eliakim R. Overcoming barriers to colorectal cancer screening tests. *IMAJ Isr Med Assoc J* 2008; 10 (8-9): 621-6.
- Fazio L, Cotterchio M, Manno M, McLaughlin J, Gallinger S. Association between colonic screening, subject characteristics, and stage of colorectal cancer. *Am J Gastroenterol* 2005; 100 (11): 2531-9.
- Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. *JAMA* 2002; 287 (3): 321-8.
- Berends FJ, Kazemier G, Bonjer HJ, Lange JF. Subcutaneous metastases after laparoscopic colectomy. *Lancet* 1994; 344 (8914): 58.
- Fleshman J, Sargent DJ, Green E, et al. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. *Ann Surg* 2007; 246 (4): 655-62; discussion 662-4.
- Jayne DG, Guillou PJ, Thorpe H, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *J Clin Oncol* 2007; 25 (21): 3061-8.
- Lacy AM, Delgado S, Castells A, et al. The long-term results of a randomized clinical trial of laparoscopy-assisted versus open surgery for colon cancer. *Ann Surg* 2008; 248 (1): 1-7.
- Bleiberg H. Adjuvant treatment of colon cancer. *Curr Opin Oncol* 2005; 17 (4): 381-5.
- Avital S, Kashtan H, Hadad R, Werbin N. Survival of colorectal carcinoma in the elderly. A prospective study of colorectal carcinoma and a five-year follow-up. *Dis Colon Rectum* 1997; 40 (5): 523-9.
- Gross CP, Andersen MS, Krumholz HM, McAvay GJ, Proctor D, Tinetti ME. Relation between Medicare screening reimbursement and stage at diagnosis for older patients with colon cancer. *JAMA* 2006; 296 (23): 2815-22.
- Cress RD, Morris C, Ellison GL, Goodman MT. Secular changes in colorectal cancer incidence by subsite, stage at diagnosis, and race/ethnicity, 1992-2001. *Cancer* 2006; 107 (5 Suppl): 1142-52.
- Cucino C, Buchner AM, Sonnenberg A. Continued rightward shift of colorectal cancer. *Dis Colon Rectum* 2002; 45 (8): 1035-40.
- Kapiteijn E, Marijnen CA, Nagtegaal ID, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; 345 (9): 638-46.
- Swedish Rectal Cancer Trial (SRCT). Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; 336 (14): 980-7.
- Moloo H, Sabri E, Wassif E, et al. Laparoscopic resection for colon cancer: would all patients benefit? *Dis Colon Rectum* 2008; 51 (2): 173-80.
- Bonjer HJ, Hop WC, Nelson H, et al. Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. *Arch Surg* 2007; 142 (3): 298-303.
- Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst* 2007; 99 (6): 433-41.
- Samantas E, Dervenis C, Rigatos SK. Adjuvant chemotherapy for colon cancer: evidence on improvement in survival. *Dig Dis* 2007; 25 (1): 67-75.
- Grinnel RS. Results of ligation of inferior mesenteric artery at the aorta in resections of carcinoma of the descending colon and rectum. *Surg Gynecol Obstet* 1965; 120: 1031-6.
- Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer: a population-based study. *Ann Surg* 2006; 244 (4): 602-10.
- Brenner H, Gondos A, Arndt V. Recent major progress in long-term cancer patient survival disclosed by modeled period analysis. *J Clin Oncol* 2007; 25 (22): 3274-80.
- Verdecchia A, Francisci S, Brenner H, et al. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. *Lancet Oncol* 2007; 8 (9): 784-96.

Pheochromocytoma: Progress and Challenges

Yehonatan Sharabi MD FAHA

Hypertension Unit, Sheba Medical Center, Tel Hashomer affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

KEY WORDS: pheochromocytoma, bladder, hypertension, metanephrines

IMAJ 2011; 13: 304–305

Pheochromocytoma is a rare cause of hypertension but is often sought in the workup of secondary hypertension in appropriate subjects, since such a diagnosis provides an opportunity to offer definitive treatment for a disease that is otherwise incurable in most cases and involves chronic use of multiple medications.

Despite progress over the last decade in our ability to detect, localize and treat pheochromocytoma, the most important aspect remains the initial clinical suspicion. In their report in this issue of *IMAJ*, Zeitlin et al. [1] present the case of a malignant paraganglioma of the bladder in a patient with a 12-year history of hypertension and a few incidents of life-threatening hypertensive crises. Once the patient was under their care, the clinical suspicion of pheochromocytoma was raised and a series of biochemical and imaging procedures followed which confirmed the diagnosis.

The typical triad of severe headache, palpitations and diaphoresis accompanying episodes of high blood pressure should lead one to suspect pheochromocytoma. Nevertheless, most subjects with this combination do not have a pheochromocytoma. Several clinical conditions can mimic pheochromocytoma; the most typical mimicking condition is pseudopheochromocytoma [2]. This condition is related to increased adrenoceptor sensitivity rather than increased

circulating catecholamines. Therefore, the most important first step is to rule out pheochromocytoma.

Over the last decade data have accumulated with regard to the role of free plasma metanephrines as a screening test for this condition [3,4]. This test has essentially 100% sensitivity in symptomatic patients, which means an ideal negative predictive value and no further workup is needed after a single blood test. In centers where this test is not available, repeated (twice) normal 24-hour urinary collections for both metanephrines and catecholamines have a 95% negative predictive value. Other biochemical tests such as urinary VMA (vanillylmandelic acid) have low sensitivity and should be abandoned since they have no role in the decision-making process.

It is important to note that plasma metanephrines can be relied on only if determined by HPLC (high-performance liquid chromatography) or LCMS (liquid chromatography-mass spectrometry). All other commercially available kits for plasma metanephrines do not have sufficient sensitivity for the purpose of ruling out pheochromocytoma definitively because of detection of conjugated as well as free metanephrines.

Positive results of the screening tests are followed by confirmatory tests. Until recently clonidine suppression and glucagon stimulation tests were used [5]. Glucagon exerts a specific effect on pheochromocytoma cells and not normal chromaffin cells [6]. However, in a study of 64 subjects, half with pheochromocytoma, we found that it adds very little to the clonidine suppression test; on the other hand, injecting glucagon can elicit a severe increase in blood pressure [7]. Therefore, the glucagon test should also be aban-

doned for confirming the diagnosis of pheochromocytoma, but the clonidine suppression test can be used.

With regard to localization, Zeitlin et al. [1] listed the various options of imaging studies. One must ensure that if a CAT scan is ordered for the localization of a tumor the request should specifically note “fat suppressed.” This allows the radiologist to provide the maximum information from the imaging study. To look for primary tumors and metastases ¹²³I-MIBG scanning is indicated. A negative scan does not exclude pheochromocytoma, however. The authors mention ¹⁸F-dopamine positron emission tomography scanning, but this is currently available only at the U.S. National Institutes of Health and is a research test. An alternative is ¹⁸FDG PET scanning, which together with positive biochemical results make the diagnosis of pheochromocytoma very likely and can serve as a means to exclude the presence of metastases when surgery is considered.

In the case presented here the pathological diagnosis was paraganglioma. Paraganglioma shares many features with pheochromocytoma, both clinically and pathogenetically. It is indeed a neuroendocrine tumor arising from the sympathetic nervous system, but unlike pheochromocytoma its cells are negative for chromaffin. It is usually found in the neck, most commonly from the carotid body, and only in rare reported cases was paraganglioma found in other sites, such as in the mediastinum and abdominal cavity. Paraganglioma of the urinary bladder is extremely rare. Malignant paraganglioma is also rare. Malignant paragan-

¹⁸FDG-PET = fluorodeoxyglucose-positron emission tomography

glioma of the bladder is therefore exceedingly rare, and the diagnosis was made solely because of clinical suspicion and the appropriate workup by Drs. Zeitlin and colleagues.

Future studies are now directed at exploring the molecular basis of the various forms of pheochromocytoma. We hope that this new avenue will lead to the development of better strategies to detect and treat malignant pheochromocytoma where we often fail, as this challenging case demonstrates.

Corresponding author:

Dr. Y. Sharabi

Head, Hypertension Unit, Sheba Medical Center, Tel Hashomer 52621, Israel

Fax: (972-3) 535-5428

email: SharabiY@sheba.health.gov.il

References

1. Zeitlin I, Dessau H, Lorberboym M, Beigel Y. Malignant pheochromocytoma of the urinary bladder: challenges in diagnosis and management. *IMAJ Isr Med Assoc J* 2011; 13: 311-13.
2. Sharabi Y, Goldstein DS, Benth O, et al. Sympathoadrenal function in patients with paroxysmal hypertension: pseudopheochromocytoma. *J Hypertens* 2007; 25 (11): 2286-95.
3. Goldstein DS, Eisenhofer G, Flynn JA, Wand G, Pacak K. Diagnosis and localization of pheochromocytoma. *Hypertension* 2004; 43 (5): 907-10.
4. Lenders JW, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA* 2002; 287 (11): 1427-34.
5. Grossman E, Goldstein DS, Hoffman A, Keiser HR. Glucagon and clonidine testing in the diagnosis of pheochromocytoma. *Hypertension* 1991; 17 (6 Pt 1): 733-41.
6. Sharabi Y, Zimlichman R, Alesci S, et al. Glucagon does not affect catecholamine release in primary cultures of bovine adrenal chromaffin cells. *Horm Metab Res* 2005; 37 (4): 205-8.
7. Lenders JW, Pacak K, Huynh TT, et al. Low sensitivity of glucagon provocative testing for diagnosis of pheochromocytoma. *J Clin Endocrinol Metab* 2010; 95 (1): 238-45.

Capsule

HLA-DPB1-COL11A2 and three additional xMHC loci are independently associated with RA in a UK cohort

Orozco et al. investigated the complex association pattern of the extended major histocompatibility complex (xMHC) region with rheumatoid arthritis (RA) susceptibility to identify effects independent of *HLA-DRB1*. High-resolution *HLA-DRB1* typing was performed. The subjects, 1804 RA cases and 1474 controls, were genotyped for 1546 single-nucleotide polymorphisms (SNPs) using Affymetrix GeneChip 500K as part of the Wellcome Trust Case Control Consortium Study. To avoid confounding by RA-associated *HLA-DRB1* alleles, the authors analyzed xMHC SNPs using a data set with pairwise matching of cases and controls on *DRB1* genotypes. A total of 594 case-control pairs with identical *DRB1* genotypes were identified. After this adjustment, 104 SNPs remained significantly associated with RA, suggesting

that additional RA loci independent of *HLA-DRB1* can be found in the xMHC region. Of these, four loci showed the strongest associations with RA: *ZNF391*, the olfactory receptor (OR) gene cluster, *C6orf26-RDBP* and *HLA-DPB1-COL11A2*. An additional locus mapping to the *BTN* (butyrophilin) cluster showed independent association with RA in anti-cyclic citrullinated peptide-positive patients exclusively. The investigators validated the previously described independent association of the *HLA-DPB1-COL11A2* locus with RA. In addition, association with three novel independent RA loci in the xMHC region (*ZNF391*, *OR2H1* and *C6orf26-RDBP*) was detected.

Genes Immun 2011; 12: 169
Eitan Israeli

Capsule

Blood cells as signs for heart transplant rejection

Recipients of heart transplants are treated with powerful immunosuppressants to prevent organ rejection, but complications still occur. Early signs of rejection are often monitored by an invasive procedure that requires heart tissue biopsy. A non-invasive diagnostic test was recently approved in the United States, in which blood cells from heart transplant recipients are monitored for the expression of genes associated with immune-mediated rejection. Snyder et al. have designed a potentially complementary non-invasive test based on the concept that during organ rejection, dying cells in the organ release donor DNA that might be detectable in the recipient's bloodstream by high-throughput

sequencing methods. In a small proof-of-principle study of archived blood samples from heart transplant recipients, the authors showed that the level of cell-free donor DNA in the recipient's blood increased substantially when there was an acute cellular rejection episode and then declined again once the patient received more aggressive treatment. Although an encouraging start, the predictive value of this test will become clear only from much larger studies in which its performance is compared with that of biopsies and with conventional clinical measures of heart function, such as echocardiograms.

Proc Natl Acad Sci USA 2011; 108: 6229
Eitan Israeli

“Gentlemen, we have run out of money. Now we have to think”

Winston Churchill (1874-1965), British politician, statesman, writer and orator

Cardiopulmonary Resuscitation in the Pregnant Patient – An Update

Tiberiu Ezri MD^{1,4}, Shmuel Lurie MD², Carolyn F. Weiniger MB ChB³, Abraham Golan MD FRCOG² and Shmuel Evron MD^{1,4}

Departments of ¹Anesthesia and ²Obstetrics & Gynecology, Wolfson Medical Center, Holon, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

³Department of Anesthesiology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

⁴Outcomes Research Consortium, Cleveland, Ohio, USA

KEY WORDS: cardiac arrest, pregnancy, etiology, management, cardiopulmonary resuscitation (CPR)

IMAJ 2011; 13: 306–310

Cardiac arrest in pregnancy is a rare encounter, considered to occur in 1:30,000 births [1]. It may lead to perimortem cesarean delivery in order to save the mother and her infant [2].

“Five minutes is just about long enough, depending upon personal preference, to boil an egg and butter some toast. It is also the period of time during which obstetric care givers are expected to identify maternal cardiac arrest, initiate cardiopulmonary resuscitation and, if maternal cardiac output is not immediately restored, deliver the fetus by caesarean section.” [3]. This quotation is a quintessence of the complexity involved in providing high-quality medical care quickly and efficiently to the pregnant patient who suffers a cardiac arrest.

Following their analysis of an anonymous questionnaire survey among obstetricians, anesthesiologists and midwives, Einav et al. [4] concluded that specialist clinicians who treat pregnant women in hospital on a daily basis possess a limited knowledge of the recommendations for treating maternal cardiac arrest. This review is therefore intended to update the readers' knowledge with regard to cardiopulmonary resuscitation in pregnant patients. We start with a brief presentation of a real case and follow with a review of the pathophysiology and etiology of CA in pregnancy, with special emphasis on the anesthetic causes of CA and management strategies. A brief description of CPR in pregnancy is also included, and the importance of emergency delivery (hysterotomy or cesarean delivery) is emphasized.

CA =cardiac arrest

CPR = cardiopulmonary resuscitation

CASE REPORT

A 35 year old, 38 weeks pregnant, apparently healthy woman was referred by her family physician urgently to our labor and delivery unit due to concern about her lack of appetite over the past week and her altered mood. Her 15 year old son confirmed that she appeared depressed and had not left the house for the past week. Her communication difficulties were attributed to her new immigrant status in Israel. She appeared exhausted with low mood. At this stage there was no specific diagnosis. Upon admission to the hospital her vital signs were stable: blood pressure 120/70 mmHg, heart rate 70 beats/minute and oxygen saturation 98% on room air. Fetal heart rate tracing was also normal. She was not in active labor and did not complain of pain. The on-duty anesthesiologist was asked to consult the patient regarding epidural analgesia once in active labor. The patient appeared confused and uncooperative, and approximately 10 minutes after the history-taking and examination had begun the patient developed witnessed cardiorespiratory arrest (asystole). This was accompanied by severe fetal bradycardia. CPR in the left tilt position was immediately started by the resident anesthesiologist and the obstetrician. The operating room was prepared for an emergency cesarean delivery. The left tilt was achieved with a rolled blanket placed under the patient's right hip and lumbar area.

The alerted in-house senior obstetrician, anesthesiologist and neonatologist arrived at the scene within 2 minutes. The

Some reasons for cardiac arrest in pregnancy are reversible and should be recognized and managed promptly

patient's trachea was intubated while receiving cardiac massage at a rate of 100/min, 10 breaths/min and two intravenous boluses of 1 mg each of atropine and epinephrine. Spontaneous circulation and normal blood pressure resumed after 2 minutes of CPR, but the patient remained unconscious with both pupils dilated and unreactive to light. Approximately 5 minutes after the diagnosis of CA, an emergency cesarean delivery was performed in the operating room which was situated inside the delivery unit. The patient remained unresponsive (no movement, with unchanged heart rate and blood pressure) to the surgical

stimulus. The patient received no anesthesia and only 100 µg IV fentanyl for analgesia, with no muscle relaxants. The baby was delivered with an Apgar score of 4/6 and a pH of 7 and his condition gradually improved during the following hours. Following the cesarean delivery the mother remained unresponsive, with a Glasgow Coma Scale of 3. A brain computed tomography scan revealed severe diffuse brain edema. The patient was treated with mild hyperventilation, mannitol, rest in a semi-recumbent position and oxygen to keep her oxygen saturation above 98%. Following resolution of some brain edema, a huge frontal herniated brain tumor was revealed. The tumor was considered inoperable and the patient died 5 days later.

This case emphasizes that CPR skills may be required unexpectedly in the labor ward and that management of cardiac arrest involves prompt initiation of the correct treatment, which could include cesarean delivery and treatment of the underlying cause of the CA [3,4].

PATHOPHYSIOLOGY OF CARDIAC ARREST IN PREGNANCY

In pregnant women, CA is complicated by the pathophysiological changes that occur during pregnancy, especially aortocaval compression. During CPR with closed chest massage in non-pregnant patients the maximal cardiac output approximates 30% of normal [5]. In patients ≥ 20 weeks pregnant lying in the supine position, the cardiac output is further decreased. This implies that if these patients suffer CA when placed in the supine position, there will be practically no cardiac output at all despite a correctly performed CPR.

Patients in advanced pregnancy also have a tendency for rapid development of hypoxemia and acidosis, a higher risk of pulmonary aspiration, and an increased incidence of difficult intubation as compared to the non-pregnant population. These changes are exaggerated by multiple pregnancy and obesity, all of which make the resuscitation more difficult.

ETIOLOGY AND DIFFERENTIAL DIAGNOSIS OF CARDIAC ARREST IN PREGNANCY

It is imperative to identify reversible causes of CA. The age of pregnancy should be quickly established in order to decide on fetal viability. Abdominal ultrasound examination is used for this purpose but it should not delay resuscitation procedures.

The etiology of CA in pregnancy can be classified into anesthesia-related causes and/or non-anesthesia-related causes [Tables 1 and 2]. Occasionally, the etiology is multifactorial, making the diagnosis and management more challenging.

ANESTHESIA-RELATED MATERNAL MORTALITY

The 1990-2003 USA closed claims data in obstetric anesthesia reported 69 cases of anesthesia-related death or severe brain injury; 18% (vs. 6.7% in the non-pregnant surgical population) were linked to airway problems. Airway catastrophes were also related to some poor fetal outcomes [8].

It is noteworthy that through the decades, a change in anesthesia-related maternal mortality trends has been observed. Around 40 years ago, the aspiration of gastric contents was the leading cause of anesthesia-related maternal death, but in the following 20 years the culprit was failed intubation. More recently, attention to airway loss during induction of anesthesia has led to a decrease in airway mortality during induction. However, mortality related to airway problems during extubation of the trachea has increased, as has spinal anesthesia-related mortality [9,10].

The last Confidential Enquiries into Maternal and Child Health (CEMACH) in the United Kingdom 2003-05 reported that in six cases maternal death was directly related to anesthesia, a similar figure to that reported in 2000-02. There were three cases of postoperative airway loss: all occurred in morbidly obese parturients [11]. Twenty-seven percent of all maternal deaths (directly or indirectly related to anesthesia) occurred among obese women (body mass index > 30 kg/m²), whereas 24% occurred among overweight women (BMI > 25 kg/m²).

BMI = body mass index

Cardiopulmonary resuscitation follows general ACLS guidelines with several modifications for pregnant women, taking into account the lives of both mother and fetus

Table 1. Etiology, mechanism, characteristics and management of anesthesia-related CA in pregnancy

Category	Mechanism	Characteristics	Management
Anoxic/hypoxic	Failure to oxygenate due to failed intubation/ventilation and/or aspiration of gastric contents	<ul style="list-style-type: none"> • Obese patients • Other reasons for difficult airway 	Rescue airway procedures
Hemodynamic/Respiratory	High/total spinal (see below: specific mechanisms)	<ul style="list-style-type: none"> • Local anesthetic overdose • "Barbotage" of the CSF • Unrelieved aortocaval compression 	Hemodynamic & respiratory support
Toxicity	Local anesthetic toxicity (overdose or IV injection)	<ul style="list-style-type: none"> • Specific symptoms • Neurologic signs • Hemodynamic signs • Respiratory arrest 	Hemodynamic & respiratory support, Intralipid® (Pharmacia & Upjohn)

Table 2. Etiology, mechanism, characteristics and management of non-anesthesia-related CA in pregnancy

Category	Mechanism	Characteristics	Management
Hemodynamic	Hemorrhagic	<ul style="list-style-type: none"> • Placenta accreta, increta, percreta, previa, abruptio • Uterine rupture 	Balloons into the hypogastric arteries Surgery Fluid & blood resuscitation Management of coagulopathies
Hemodynamic	Acute coronary syndromes	<ul style="list-style-type: none"> • Smokers and older aged-pregnant women are at higher risk 	Percutaneous coronary reperfusion is the strategy of choice for ST- elevation myocardial infarction
Hemodynamic	Rupture of aortic aneurysm	Marfan syndrome & hypertensive patients [ref. 6]	Surgery if indicated
Hemodynamic /neurologic	Stroke	<ul style="list-style-type: none"> • Rupture of brain aneurysm • Embolic event • Uncontrolled hypertension 	Surgery if indicated Successful use of fibrinolytics in massive, life-threatening ischemic stroke
Hemodynamic	Air embolism	Uterus above the level of right atrium and hypovolemia	Level the table Fluid resuscitation
Toxicity	Magnesium	Overdose, particularly in oliguric patients	Calcium gluconate IV (30 ml in 10% solution)
Complex	Amniotic fluid embolism [ref. 7]	Dramatic evolution with high morbidity/mortality	Life support measures Activated factor VII Inhalation of prostacyclin or nitric oxide Extracorporeal membrane oxygenation Cardiopulmonary bypass
Complex	Pulmonary embolism	<ul style="list-style-type: none"> • Usually postoperative • Antiphospholipid antibody syndrome at high risk 	Anticoagulants in at-risk patients – problematic regional anesthesia Successful use of fibrinolytics for massive, life-threatening pulmonary embolism
Complex	Trauma	Important cause of maternal & fetal mortality	Aortocaval decompression Early CS/hysterotomy may be life-saving
Complex	Preeclampsia/eclampsia	<ul style="list-style-type: none"> • Diffuse organ impairment/ failure affecting maternal & fetal mortality • Possible airway problems 	Magnesium Antihypertensive medication Early epidural placement
Complex	Sepsis	<ul style="list-style-type: none"> • Chorioamnionitis • Pneumonia • Epidural abscess 	Antibiotics Fluid resuscitation Vasopressors
Complex	Status asthmaticus [ref 2]	<ul style="list-style-type: none"> • Airway obstruction 	Cardiopulmonary resuscitative measures Specific management of status asthmaticus

Two obese patients died in early pregnancy due to failure in managing their airway adequately. One death was caused by bupivacaine toxicity due to accidental IV infusion of bupivacaine. Thirty-one fatal cases of indirect anesthetic deaths were attributed to poor recognition and management of critical situations (bleeding, sepsis, etc).

CA AND CARDIOVASCULAR COLLAPSE AFTER SPINAL/EPIDURAL ANALGESIA/ANESTHESIA

This scenario could occur following spinal analgesia in multiple gestation, obesity, “barbotage” of the cerebrospinal fluid, subdural block, spinal overdose, repeated spinal/epidural blocks, spinal injection following “failed” epidural, epidural overdose, toxic reaction to local anesthetic overdose, or intravascular injection.

High spinal block in pregnancy can be successfully managed by early recognition and aggressive treatment. Management includes left uterine displacement. Fluids are rapidly infused while bradycardia is aggressively treated with atropine or epinephrine and hypotension should be treated with phenylephrine or epinephrine. Oxygen 100% should be administered by mask,

or if necessary endotracheal intubation can be performed with cricoid pressure.

CARDIAC ARREST IN PREGNANCY – ADVANCED CARDIAC LIFE SUPPORT GUIDELINES

The following are updated guidelines [5,12] for which there are several modifications for pregnant women, taking into account the lives of both mother and fetus since fetal survival depends on maternal survival.

Key interventions for managing cardiac arrest in pregnant women:

- First responder or single rescuer will start CPR with chest compression (CAB instead of ABC)
- Place the woman in left lateral position
- Ventilate the patient with 100% oxygen
- Establish IV access and administer fluids using upper extremity veins

CAB = circulation airway breathing
 ABC = airway breathing circulation

- Consider the possible cause of cardiac arrest to ease targeted management

1. Left lateral position

Place the patient on a hard surface in 15°-30° left lateral tilt position or pull the uterus to the side. The left tilt can be achieved manually or with a rolled blanket under the right hip and lumbar area.

2. Airway and breathing

Apply continuous cricoid pressure during ventilation and intubation due to the risk of regurgitation. Consider the possibility of airway edema especially in parturients with gestational hypertension which can make endotracheal intubation difficult. Start with two rescue breaths of one second each. Bag-mask ventilate at a rate of 8-10 breaths/min and a tidal volume large enough to raise the chest, during pauses of compressions (synchronization). Synchronization between chest compressions and ventilation is not necessary with an advanced airway (endotracheal tube) in place. It must be noted that hyperventilation is harmful and should be avoided.

3. Circulation

Chest compressions are performed higher than in non-pregnant patients, slightly above the center of the sternum due to the elevated diaphragm and abdominal contents. Chest compressions should be performed with the patient lying on a hard surface. “Push fast and hard”! Place the heel of one hand on the center of the chest. Place the other hand on top. Interlock the fingers and compress the chest at a rate of 100/min, a depth of 4-5 cm and equal compression:relaxation times. It is recommended that the CPR operator be changed every 2 minutes. Although vasopressors (epinephrine, vasopressin) reduce blood flow to the uterus, current recommendations advise using standard drugs in standard adult ACLS doses. A single dose of vasopressin 40 units is an alternative to repeated epinephrine injection. Amiodarone 300 mg IV has replaced lidocaine for treatment of ventricular arrhythmias.

4. Compression-ventilation (C-V) ratio

A C-V ratio of 30:2 is recommended. With two or more rescuers switch the compressor every 2 minutes or every five cycles of C-V. In the newborn give two ventilations after 15 compressions (C-V ratio of 15:2) if the etiology of CA is cardiac or a ratio of C-V 3:1 if the etiology is respiratory.

5. Defibrillation

Standard ACLS defibrillation doses should be used. Survival rates are highest with immediate CPR and defibrillation within 3 to 5 minutes of a witnessed pulseless ventricular tachycardia or fibrillation. Defibrillation is administered at the following doses:

- Monophasic – 360 joules (J)
- Biphasic – *truncated exponential waveform* 150-200 J
- Biphasic – *rectilinear waveform*: 120 J
- Newborn – 2 J/kg for the first attempt and 4 J/kg for subsequent attempts
- The ACLS guidelines emphasize the importance of availability of automated external defibrillators.

Electric cardioversion during pregnancy has been described in the literature and appears to be safe for the fetus [13].

In pregnant women a secondary reassessment of the airway and breathing is critical to consider early intubation owing to the risk of aspiration. The endotracheal tube size should be smaller and the correct position should be confirmed with capnography.

Incorrectly applied cardiac compressions in pregnant patients with CA may be complicated with liver laceration, uterine rupture, hemothorax and hemopericardium.

Successful cardiopulmonary resuscitation (CPR) implies early recognition of cardiac arrest, aortocaval decompression, early hysterotomy/cesarean delivery and acquiring CPR skills by the managing teams

EMERGENCY DELIVERY

If cardiac arrest is not immediately (4-5 minutes) reversed by basic and advanced life support, emergency hysterotomy (or cesarean delivery) should be performed at > 20 pregnancy weeks. The best survival rate for an infant is at age > 24 or 25 weeks if delivered < 5 minutes after CA [14]. Gestational age may not always be known and ultrasonography can be used if time permits. It is important to recognize that a promptly performed cesarean delivery may save the mother and her infant.

Timely hysterotomy delivers the fetus, empties the uterus, restores venous return and aortic flow and, in addition, allows newborn resuscitation. Cesarean section might be necessary to accomplish a successful resuscitation even if the fetus has died.

Immediately following the diagnosis of CA, a well-trained team comprising a gynecologist, anesthesiologist, neonatologist and midwives should activate the departmental hysterotomy protocol, in parallel with the CPR efforts. This requires preparation of the operating room for an emergency hysterotomy which ideally should be performed no longer than 4-5 minutes after initiation of CPR.

CONCLUSIONS

Cardiac arrest is a rare, unexpected and devastating event for pregnant patients and those treating them. Early anticipation

ACLS = Advanced Cardiac Life Support
C-V = compression-ventilation

and treatment may prevent CA, for example following high spinal block. Multidisciplinary teams should be familiar with the ACLS guidelines and their special modifications for pregnant women. In addition, there should be a well-conceived hysterotomy protocol in delivery rooms, which should be fully equipped for both resuscitation and emergency hysterotomy within 4-5 minutes.

Corresponding author:

Dr. T. Ezri

Head, Dept. of Anesthesia, Wolfson Medical Center, Holon 58100, Israel

Phone: (972-3) 502-8229

Fax: (972-3) 502-8843

email: ezri@wolfson.health.gov.il

References

- Morris S, Stacey M. Resuscitation in pregnancy. *BMJ* 2003; 327: 1277-9.
- Lurie S, Mamet Y. Cesarean delivery during maternal cardiopulmonary resuscitation for status asthmaticus. *Emerg Med J* 2003; 20: 296-7.
- Banks A. Maternal resuscitation: plenty of room for improvement. *Int J Obstet Anesth* 2008; 17: 289-91.
- Einav S, Matot I, Berkenstadt H, Bromiker R, Weiniger CF. A survey of labour ward clinicians' knowledge of maternal cardiac arrest and resuscitation. *Int J Obstet Anesth* 2008; 17: 238-42.
- 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2005; 112 (Issue 24 Suppl); December 13.
- Elkayam U, Ostrzega E, Shotan A, Mehra A. Cardiovascular problems in pregnant women with the Marfan syndrome. *Ann Intern Med* 1995; 123: 117-22.
- Conde-Agudelo A, Romero R. Amniotic fluid embolism: an evidence-based review. *Am J Obstet Gynecol* 2009; 201: 445.e1-13.
- Davies JM, Posner KL, Lee LA, Cheney FW, Domino KB. Liability associated with obstetric anesthesia: a closed claims analysis. *Anesthesiology* 2009; 110: 131-9.
- Arendt KW. Present and emerging strategies for reducing anesthesia-related maternal morbidity and mortality. *Curr Opin Anaesth* 2009; 22: 330-5.
- Mhyre JM, Riesner MN, Polley LS, Naughton NN. A series of anesthesia-related maternal deaths in Michigan, 1985-2003. *Anesthesiology* 2007; 106: 1096-104.
- Cooper GM, McClure JH. Anaesthesia chapter from Saving Mothers' Lives; reviewing maternal deaths to make pregnancy safer. *Br J Anaesth* 2008; 100: 17-22.
- Sinz E, Lavonas EJ, Jeejeebhoy FM. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 12: Cardiac arrest in special situations. *Circulation* 2010; 122: S829-61.
- Nanson J, Elcock D, Williams M, et al. Do physiological changes in pregnancy change defibrillation energy requirements? *Br J Anaesth* 2001; 87: 237-9.
- Katz V, Balderston K, DeFreest M. Perimortem cesarean delivery: were our assumptions correct? *Am J Obstet Gynecol* 2005; 192: 1916-20; discussion 1920-1.

Capsule

The helminth product ES-62 protects against septic shock via Toll-like receptor 4-dependent autophagosomal degradation of the adaptor MyD88

Sepsis is one of the most challenging health problems worldwide. Puneet et al. found that phagocytes from patients with sepsis had considerable up-regulation of Toll-like receptor 4 (TLR4) and TLR2; however, shock-inducing inflammatory responses mediated by these TLRs were inhibited by ES-62, an immunomodulator secreted by the filarial nematode *Acanthocheilonema viteae*. ES-62 subverted TLR4 signaling to block TLR2- and TLR4-driven inflammatory responses via autophagosome-mediated down-regulation of the TLR adaptor-transducer MyD88. In vivo, ES-62

protected mice against endotoxic and polymicrobial septic shock by TLR4-mediated induction of autophagy and was protective even when administered after the induction of sepsis. Given that the treatments for septic shock at present are inadequate, the autophagy-dependent mechanism of action by ES-62 might form the basis for urgently needed therapeutic intervention against this life-threatening condition.

Nature Immunol 2011; 12: 344

Eitan Israeli

Capsule

SIK2 degradation after ischemia is beneficial to neurons

The transcription factor cAMP responsive element-binding protein (CREB) mediates neuroprotection after stroke. Sasaki et al. identified a cell-signaling pathway that modulates CREB activation after ischemia. CREB activity can be controlled by recruitment of stimulatory cofactors such as transducer of regulated CREB activity-1 (TORC1). In cell culture experiments, the researchers showed that TORC1 translocation to the nucleus was increased after ischemia and was required for activation of CREB. TORC1 over-expression could reduce neuron death in response to ischemia. TORC1 is phosphorylated by salt-inducible kinase-2 (SIK2), which was degraded in cultured neurons after

ischemia, and SIK2 phosphorylation by Ca²⁺/calmodulin-dependent protein kinases seemed to be responsible for this process. Increasing SIK2 expression prevented TORC1 from entering the nucleus and from activating CREB, and this enhanced cell death after ischemia. The researchers found that a SIK2 inhibitor could enhance CREB activity and prevent neuron death in response to ischemia, and SIK2-deficient mice were protected from stroke. These findings suggest that SIK2 degradation after ischemia is beneficial to neurons.

Neuron 2011; 13: 106

Eitan Israeli

Malignant Pheochromocytoma of the Urinary Bladder: Challenges in Diagnosis and Management

Inna Zeitlin MD¹, Hanan Dessau MD¹, Mordechai Lorberboym MD² and Yitzhak Beigel MD¹

Departments of ¹Medicine D and ²Nuclear Medicine, Wolfson Medical Center, Holon, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

KEY WORDS: extra-adrenal pheochromocytoma, urinary bladder, [¹²³I] metaiodobenzylguanidine (MIBG) scintigraphy, 6-[¹⁸F] fluorodopamine PET scan, [¹³¹I] metaiodobenzylguanidine (MIBG) treatment

IMAJ 2011; 13: 311–313

For Editorial see page 304

Pheochromocytoma may be either benign or malignant. These tumors produce and excrete significant amounts of catecholamines and their metabolites, thus giving rise to the well-known clinical picture of pheochromocytoma. If unrecognized, it may lead to death as the result of hypertensive crisis, arrhythmia or myocardial infarction. Therefore, a high index of suspicion is crucial for early diagnosis. We describe a case of malignant extra-adrenal paraganglioma, focusing on new modalities for its diagnosis and management.

PATIENT DESCRIPTION

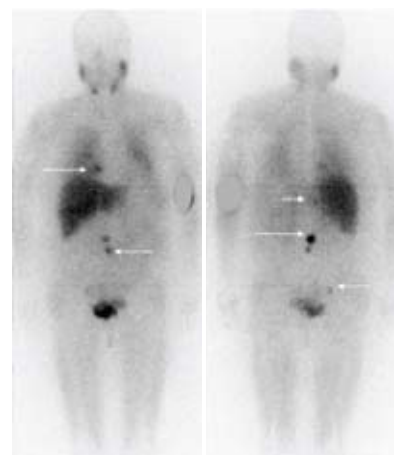
A 69 year old woman, a Russian immigrant, was hospitalized in 2006 because of recurrent syncope and episodes of severe headaches, dizziness and palpitations that had begun a few months earlier. Her medical history was remarkable for a 12-year hypertension that was relatively well controlled until 3 years before the current hospitalization. During those 3 years she experienced frequent paroxysms of severe hypertension, with blood pressure elevation up to 240/120 mmHg, which did not respond well to medical therapy despite

multiple anti hypertensive drugs. A cholecystectomy performed 3 years before the current admission was complicated by a severe life-threatening hypertensive crisis. Also noteworthy was urinary bladder neoplasm of unclear pathology that was diagnosed 8 years before the admission. At that time she was living in Russia and was treated with radiotherapy and chemotherapy. Computed tomography, performed one year before hospitalization, revealed a 6.5 cm mass in the right bladder wall. Repeated cystoscopies and biopsies demonstrated irritated mucosa with no evidence of malignancy.

On admission blood pressure was 200/110 mmHg in the supine position and 100/50 mmHg on standing; pulse was 110/minutes and regular. The rest of the physical examination was unremarkable. Laboratory tests demonstrated anemia (hemoglobin 8.7 g/dl) associated with chronic disease, prerenal azotemia (urea 116 mg/dl, creatinine 2.09 mg/dl) and hypokalemia (potassium 3.14 mmol/L). An electrocardiogram showed sinus tachycardia with non-specific ST-segment and T-wave abnormalities.

During hospitalization the recurrent elevations of blood pressure up to 240/120 mmHg accompanied by dizziness, headaches and palpitations raised the suspicion of pheochromocytoma. Levels of metanephrine, vanillylmandelic acid and catecholamines in 24-hour urine collections were significantly elevated. Treatment with phenoxybenzamine was started and propranolol was added later. A total body CT showed the 6.5 cm mass in the urinary bladder as well as a new right iliac lymphadenopathy, scattered pulmonary nodules and two solid masses in the right kidney. A

Anterior and posterior whole body images of the initial MIBG study show multiple MIBG avid foci in the right lower lung, liver, mid-abdomen spine and pelvis (arrows)



[¹²³I] metaiodobenzylguanidine scanning showed multiple foci of increased uptake in the right lung, liver, abdomen and right pelvis adjacent to the bladder [Figure 1]. No pathological uptake was observed in the adrenals. A diagnosis of metastatic extra-adrenal pheochromocytoma, most likely of urinary bladder origin, was made. During surgery the external urinary mass could be only partially excised. Biopsy revealed multiple foci compatible with paraganglioma.

Therapy with 150 mCi of [¹³¹I] MIBG was initiated. The headaches, palpitations, fainting episodes and paroxysms of hypertension gradually subsided. A repeated total body CT, performed a year later, did not show changes from the previous CT. Treatment with alpha and beta-blockers continued. Blood pressure

MIBG = metaiodobenzylguanidine

was well controlled and the patient felt well for 2 years after the operation when palpitations and paroxysms of severe hypertension recurred. Again, 24-urine free catecholamines and VMA levels were markedly elevated. A [¹²³I] MIBG scan showed new metastatic foci in the left lung, liver and spine and another course of therapy with ¹³¹I-MIBG was scheduled.

COMMENT

Pheochromocytoma is a rare catecholamine-producing chromaffin cell tumor [1]. It can be sporadic or familial, the latter often being multifocal and appearing at an earlier age. Among the germline mutations are the von Hippel-Lindau gene causing the VHL syndrome, the RET gene leading to multiple endocrine neoplasia type 2, the neurofibromatosis type 1 gene associated with neurofibromatosis type 1, and the gene encoding mitochondrial succinate dehydrogenase subunit D and B associated with familial paraganglioma and pheochromocytoma.

While most pheochromocytomas are benign, malignancy accounts for up to 26–40% of all cases. There is no certain way to predict which tumors will progress to malignancy and no single histological feature alone is predictive of metastatic invasion [2]. Prognostic factors for malignancy include large size (diameter > 5 cm), local tumor extension at the time of surgery, and the DNA ploidy pattern with aneuploidy and tetraploidy having a more aggressive nature. A scoring system that combines histological, immunohistochemical and biochemical parameters was suggested to predict both the metastatic potential and the prognosis for patients with metastatic tumors [3]. In clinical practice, the only reliable criterion of malignancy is the presence of distant metastases. Since the overall 5-year survival in patients with malignant pheochromocytomas ranges from 40% to 74%, early diagnosis is of utmost importance.

VMA = vanillylmandelic acid
VHL = von Hippel-Lindau

Hypertension, occurring in 90% of patients, may be sustained or paroxysmal. It may cause encephalopathy, retinopathy, cardiomyopathy and proteinuria. A hypertensive crisis may be induced by trauma, exercise, various medications (such as antihypertensives, tricyclic antidepressants, glucagon, opiates) or surgery. The triad of headaches, palpitations and sweating should raise a high index of suspicion for pheochromocytoma. Other features are orthostatic hypotension, syncope and hyperglycemia. Aside from catecholamines and their metabolites, pheochromocytoma can also secrete various other peptides, such as parathyroid hormone-rP, ACTH, erythropoietin and interleukin-6, which contribute to clinical symptoms.

Diagnosis is confirmed by increased levels of free catecholamines and metanephrines either in urine or plasma. Urine levels, if determined during or shortly after a hypertensive crisis, have greater sensitivity. Plasma catecholamines have a sensitivity of 90% and a specificity of 95%, and plasma metanephrines are more sensitive than plasma catecholamine. The levels of chromogranin A and neuropeptide Y are increased in more than 80% of patients; however, their specificity for pheochromocytoma is low as they may be increased in other neuroendocrine tumors. Once the diagnosis is confirmed, the next step is localization by CT or magnetic resonance imaging.

Ninety-seven percent of extra-adrenal paragangliomas are found in the abdomen, mostly in the organ of Zuckerkandl, the sympathetic ganglia, or the urinary bladder. CT and MRI scans have similar sensitivity (98%–100%), but their specificity is only 70%. Therefore, functional imaging is needed to confirm that a tumor is a pheochromocytoma. Functional imaging by ¹²³I-MIBG scintigraphy (sensitivity 83–100%, specificity 95–100%), or by ¹³¹I-MIBG scintigraphy (sensitivity 77–90%, specificity 95–100%) should be performed. False positive MIBG has been reported in cases of adrenal carcinoma, adrenal adenomas and anatomic varia-

tions of the renal pelvis. False negative MIBG examinations may be expected if the patient has not stopped taking medications that interfere with MIBG uptake, and if there are tumors that have undergone necrosis. Positron emission tomography imaging with 6-[¹⁸F] fluorodopamine positron-emitting analog of dopamine is a new useful technique. In addition, as compared with ¹³¹I-MIBG, it has a lower radiation dose, and results are available on the same day in contrast to the 24–48 hour delay necessary for ¹³¹I-MIBG imaging. Somatostatin receptor scintigraphy (Octreoscan), as compared with MIBG, is more sensitive only in metastatic pheochromocytoma, but not in benign tumors. Venous sampling coupled with the measurement of catecholamine gradient, a technically difficult invasive procedure performed in a few specialized centers, should be reserved only for selected cases when all other imaging methods have failed.

Therapy is based on antihypertensive control in adjunct to anti-tumor treatment. An alpha-blocker, phenoxybenzamine, starting with 10 mg once or twice daily and increasing the dose gradually up to a 1–2 mg/kg per daily in two divided doses, is the first-choice therapy. Beta-blockers should be instituted only after alpha-blockers have been started. This sequence is important since β -blockers lead to the loss of β_2 -receptor-mediated vasodilatation and the unopposed effects of alpha-receptors cause vasoconstriction, arterial hypertension and increased afterload, causing myocardial infarction and pulmonary edema. Doxazosin, labetalol, dihydropyridine calcium channel blockers and metyrosine, may also be beneficial. After localization of the tumor, surgical removal should be performed. Symptom relief occurs in most patients with benign pheochromocytoma. Surgical treatment alone is seldom curative in malignant pheochromocytoma, but it may prolong survival by debulking, reducing metastatic spread and hormonal activity, and by removing metastases at life-threatening locations.

Other therapeutic options are radiation, by either ^{131}I -MIBG, or a radioactive somatostatin analogue, and chemotherapy. For ^{131}I -MIBG therapy to be effective, patients are chosen on the basis of significant radioisotope uptake (> 1% of the injected dose) as demonstrated during the diagnostic MIBG scans. The only limitation of this treatment is the total radiation dose to critical organs such as bone marrow. The initial ^{131}I -MIBG dose is an important factor in the response and survival rate, as patients who received high initial doses lived longer than those who received lower doses [4]. ^{131}I -MIBG therapy is generally well tolerated, may yield partial remission in 24–54% of patients and has even been reported to produce complete remission. Similar to surgery, ^{131}I -MIBG treatment alone is not curative; therefore, integration of ^{131}I -MIBG with other therapeutic modalities should be considered in progressive disease. A somatostatin analogue therapy with octreotide is based on expression of somatostatin receptor in chromaffin cell tumors. As in therapy with

^{131}I -MIBG, only patients showing a high uptake will benefit from this treatment. Hormone secretion and tumor growth have been reported to be stabilized in 25% of cases and even decreased in 20% of cases. Side effects are leukopenia and thrombocytopenia. Combined therapy of ^{131}I -MIBG and ^{177}Lu -octreotate might be more favorable and exert fewer side effects than a single high dose of ^{131}I -MIBG with its potential severe bone marrow toxicity. Novel approaches, such as somatostatin analogues, combined with anti-angiogenic factors may become the therapeutic modality of the future. Chemotherapy should be considered for patients without avidity to radionuclide treatment or when there is progression of the disease despite conventional treatment. Combination of cyclophosphamide, vincristine and dacarbazine (CVD) in malignant pheochromocytoma showed symptomatic and hormonal responses (50–100%) but only a minimal tumoral response [5]. Combinations of etoposide and cisplatin or anthracycline, CVD and cytosine arabinoside showed some

success. However, in most patients with malignant pheochromocytoma, there is no curable therapy and the prognosis is unfavorable.

Corresponding author:

Dr. I. Zeitlin

Dept. of Medicine D, Wolfson Medical Center, Holon, Israel

email: leozeit@o13.net.il

References

1. Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. *Endocr Rev* 2003; 24: 539-53.
2. Eisenhofer G, Bornstein SR, Brouwers FM, et al. Malignant pheochromocytoma: current status and initiatives for future progress. *Endocr Relat Cancer* 2004; 11: 423-6.
3. Kimura N, Watanabe T, Noshiro T, Shizawa S, Miura Y. Histological grading of adrenal and extra-adrenal pheochromocytomas and relationship to prognosis: a clinicopathological analysis of 116 adrenal pheochromocytomas and 30 extra-adrenal sympathetic paragangliomas including 38 malignant tumors. *Endoc Pathol* 2005; 16: 23-32.
4. Safford SD, Coleman RE, Gockerman JP, et al. Iodine-131 metaiodobenzylguanidine is an effective treatment for malignant pheochromocytoma and paraganglioma. *Surgery* 2003; 134: 956-63.
5. Kaltsas GA, Besser GM, Grossman AM. The diagnosis and management of advanced neuroendocrine tumors. *Endocr Rev* 2004; 25: 458-511.

Capsule

Netting neutrophils are major inducers of type 1 interferon production in pediatric systemic lupus erythematosus

Garcia-Romo et al. show that mature systemic lupus erythematosus (SLE) neutrophils are primed in vivo by type 1 interferon (IFN) and die upon exposure to SLE-derived anti-ribonucleoprotein antibodies, releasing neutrophil extracellular traps (NETs). SLE NETs contain DNA as well as large amounts of LL37 and HMGB1, neutrophil proteins that facilitate the uptake and recognition of mammalian DNA by plasmacytoid DCs (pDCs). Indeed, SLE

NETs activate pDCs to produce high levels of IFN- α in a DNA- and TLR9 (Toll-like receptor 9)-dependent manner. The results reveal an unsuspected role for neutrophils in SLE pathogenesis and identify a novel link between nucleic acid-recognizing antibodies and type 1 IFN production in this disease.

Sci Transl Med 2011; 3: 73ra20

Eitan Israeli

Capsule

Mutations and therapy in pancreatic cancer genes

Pancreatic neuroendocrine tumors (PanNETs) are aggressive human cancers that often develop silently and progress to untreatable metastatic disease prior to diagnosis. Using an exome sequencing strategy to identify recurrent somatic mutations in PanNETs, Jiao et al. found that the most commonly mutated genes, affecting nearly 45% of the tumors, encode proteins implicated in chromatin remodeling. About

15% of the tumors had mutations altering the mammalian target of rapamycin (mTOR) signaling pathway. mTOR inhibitors are already being tested as cancer therapies, so the mutational status of the PanNETs could help to identify which patients are most likely to respond to these drugs.

Science 2011; 331: 1199

Eitan Israeli

Basilar Artery Occlusion Presenting as a Tonic-Clonic Seizure

Avi Gadoth MD and Hen Hallevi MD

Department of Neurology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

KEY WORDS: vertebrobasilar disease, stroke, status epilepticus, seizure

IMAJ 2011; 13: 314–315

Stroke-associated seizures are usually due to ischemic involvement of the cerebral cortex or intracerebral hemorrhage [1]. Cases of subcortical lesions inducing stroke are less common but have been described [2]. Non-epileptic involuntary movements of the arms and legs due to ischemic lesions in the brainstem have also been reported [3]. On the other hand there are a few reports of seizures associated with ischemic lesions of the brainstem. The pathophysiology and mechanism of

such seizures are not known. We report a case of a seizure as a presenting symptom of basilar artery occlusion resulting in an ischemic stroke of the pons.

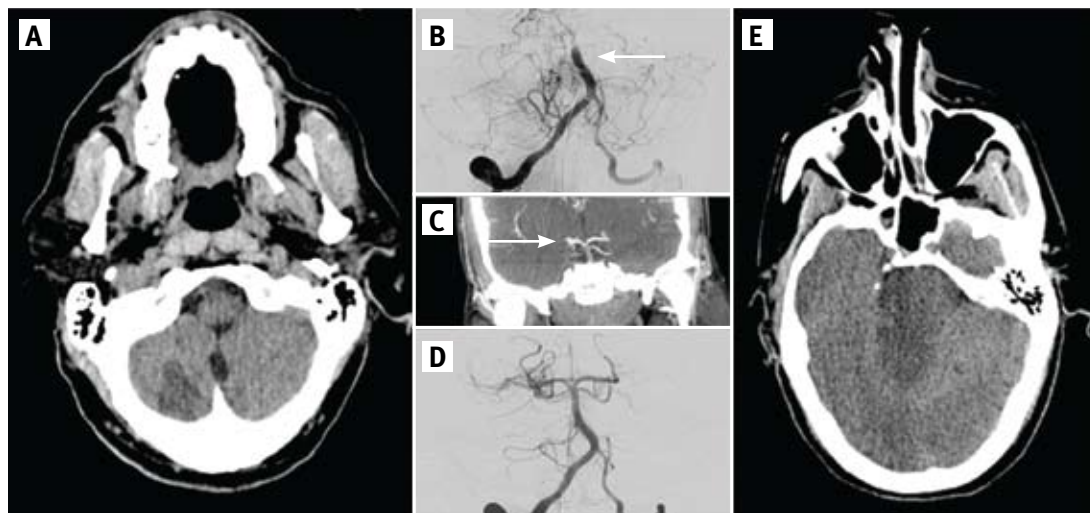
PATIENT DESCRIPTION

A 53 year old man with no history of epilepsy was admitted to the emergency department with complaints of vertigo, nausea and a single episode of vomiting. On neurologic examination eye movements were intact, there was no nystagmus or pyramidal signs, and instability of gait was noted. On computed tomography without contrast media a hypodense lesion was observed on the right cerebellum [Figure A].

Two days after admission the patient became confused. Several minutes later

the staff noticed vocalization followed by loss of consciousness and tonic-clonic movements with small amplitude in all four limbs. The presentation was seen by a neurologist who interpreted it as generalized tonic-clonic seizure, and since the condition continued for several minutes, status epilepticus was suspected. Intravenous phenytoin was administered with good seizure control at the end of the loading dose. Bedside monitor electroencephalogram performed half an hour after the movements stopped showed no epileptic activity. Urgent CT showed no hemorrhage or signs of new stroke.

Two hours from seizure onset, while the patient was regaining consciousness, right hemiplegia, right gaze limitation and Babinsky sign on the right were observed.



[A] CT of the brain after admission to the hospital showing left cerebellar stroke **[B]** A cutoff sign of the basilar artery is demonstrated on angiography **[C]** CT-angiogram of the brain after seizure showing a filling defect in the mid-basilar artery

[D] Angiogram at the end of the mechanical thrombectomy of the basilar artery occlusion showing open basilar artery **[E]** Brain CT after the procedure demonstrating large hypodense lesion in the left pons

Urgent neck and brain CT-angiography demonstrated right vertebral artery dissection and a filling defect in the mid-basilar artery [Figure C]. IV heparin was started and the patient was transferred to the angiography suite where stenting of the vertebral artery dissection and mechanical thrombectomy of the basilar artery occlusion were performed. Recanalization of the basilar artery was achieved 8 hours after seizure onset [Figure D]. Despite treatment the patient developed a large infarct in his left pons [Figure E] and remained mute, left hemiplegic and with lateral and vertical gaze palsy.

COMMENT

Seizure mechanism in the acute phase of stroke is unknown but may be related to the acute focal metabolic derangement including local acidosis, brain edema, and altered electrolyte balance and neurotransmitter activity. Although the majority of stroke-related seizures involve the cerebral cortex, there are reports of seizures as a presenting symptom of lacunar stroke [2]. Our case demonstrates generalized tonic-clonic seizure as a presenting symptom of basilar artery occlusion without evidence of cortical involvement on imaging studies.

Since recanalization was achieved within a few hours we cannot exclude the possibility of a transient occipital cortex ischemia that caused sufficient metabolic derangement for the seizures to occur. The other possibility is that contrary to the common notion, seizure is possible

without cortical involvement. In their report in 1978, Nathanson et al. [4] present four cases of patients with brainstem damage who developed seizures of axial structures; the authors hypothesized that these were epileptic seizures originating from the brainstem and not the brain cortex. The only report we found of basilar artery occlusion presenting as seizure describes two Japanese patients who were admitted with convulsions, loss of consciousness and hemiplegia [5]. Like our patient, they had brainstem, thalamic and cerebellar signs of ischemia on brain diffusion-weighted magnetic resonance imaging and no cortical involvement.

Involuntary movements at the onset of basilar artery occlusion or brainstem ischemic stroke have been described in a few papers [3]. These describe series of patients with vertebrobasilar stroke and wide clinical presentations that include fasciculation-like, shivering, jerky, tonic-clonic, and intermittent shaking movements. In all the cases EEG was normal, consciousness was preserved, and there was no effect of anti-epileptic drugs. In a review summarizing these cases [3], the conclusion was that these were non-epileptic seizures. One of the mechanisms suggested was disruption of inhibitory projection of the cortex to the spine or brainstem. In our case, although resembling these cases in some aspects such as normal EEG and no evidence of cortical involvement, the patient was unconscious, there was vocalization at the onset of movements and the convulsions stopped at the end of the loading dose of phenytoin.

In conclusion, our case demonstrates that acute basilar occlusion can present in a manner undistinguishable from generalized tonic-clonic seizure. If indeed this represents a true seizure, the mechanism may be related to occipital cortex ischemia or activation of subcortical seizure generators. Neurologists and emergency room physicians need to be aware of this and must perform a CT angiogram. Cases of atypical features of epilepsy such as basilar occlusion represent a deadly condition that may be treated if diagnosed in time. In our case the recent cerebellar stroke and the lack of seizure history in addition to the focal signs on examination provided the clues to a timely diagnosis and treatment.

Corresponding author:

Dr. H. Hallevi
 Dept. of Neurology, Tel Aviv Sourasky Medical Center, 6 Weizmann St., Tel Aviv 64239, Israel
Phone: (972-3) 697-3424
Fax: (972-3) 697-3158
email: hen.hallevi@gmail.com

References

1. Szaflarski JP, Rackley AY, Kleindorfer DO, et al. Incidence of seizures in the acute phase of stroke: a population-based study. *Epilepsia* 2008; 49: 974-81.
2. Avrahami E, Drory VE, Rabey MJ, Cohn DF. Generalized epileptic seizures as the presenting symptom of lacunar infarction in the brain. *J Neuro* 1988; 235: 472-4.
3. Saposnik G, Caplan LR. Convulsive-like movements in brainstem stroke. *Arch Neurol* 2001; 58: 654-7.
4. Nathanson M, Krumholz A, Biddle D. Seizures of axial structures. *Arch Neurol* 1978; 35: 448-52.
5. Naganuma M, Hashimoto Y, Matsuura Y, Terasaki T, Hirano T, Uchino M. Two cases of top of the basilar syndrome with onset seizure. *Rinsho Shinkeigaku* 2005; 45: 647-51.

Capsule

Genetics of candidiasis susceptibility

Chronic mucocutaneous candidiasis disease (CMCD) is characterized by chronic or recurring infection with *Candida albicans* and, to a lesser extent, with *Staphylococcus aureus*. The underlying cause of CMCD is unknown. Puel and co-researchers report two genetic etiologies associated with CMCD. The first is an autosomal recessive mutation in interleukin 17 (IL-17) receptor

A, which prevents its expression. The second is an autosomal dominant mutation in the cytokine IL-17F, which partially reduces its activity. Thus, human IL-17-mediated immunity is required for protection against these mucocutaneous infections.

Science 2011; 332: 65
 Eitan Israeli

Healing of Refractory Leg Ulcer in a Patient with Thalassemia Intermedia and Hypercoagulability after 14 Years of Unresponsive Therapy

Carina Levin MD and Ariel Koren MD

Pediatric Hematology Unit and Department of Pediatrics B, HaEmek Medical Center, Afula, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

KEY WORDS: thalassemia intermedia, leg ulcer, thrombophilia, factor V Leiden

IMAJ 2011; 13: 316–318

Chronic leg ulcers, specially in patients with thalassemia, are difficult to cure [1]. Understanding the underlying pathogenesis is crucial for successful therapy. Hypercoagulability was recently shown to contribute to the etiology and perpetuation of leg ulcers [2]. We present a patient with thalassemia intermedia, post-splenectomy with a factor V Leiden mutation and chronic leg ulcer that had not healed for 14 years.

PATIENT DESCRIPTION

A 35 year old woman with beta-thalassemia intermedia, homozygous for the IVS1,1 mutation, had suffered for 14 years from a chronic non-healing ulcer on her left leg [Figure]. The patient was diagnosed

at age one year with beta-thalassemia and received regular blood transfusions until the age of 6 when she underwent a splenectomy due to severe hypersplenism. She was then prescribed low-dose aspirin for thrombocytosis and received sporadic blood transfusions as required. She was found to be heterozygous for the factor V Leiden mutation (G1691A). All other genetic and plasmatic thrombophilic analyses were normal. No thrombotic events were ever diagnosed. Chelation therapy with deferoxamine was started at age 12; at age 21 regular blood transfusions were again required.

Her current medical treatment includes subcutaneous infusion of desferrioxamine, folic acid, low-dose aspirin, oral penicillin, allopurinol (due to hyperuricemia), calcium, vitamin α D3 and alendronate.

At age 19 the patient developed an ulcer in the internal malleoli area of the left leg [Figure]. For a year before emergence of the ulcer, her mean hemoglobin level was 6.7 g/dl and fetal hemoglobin 96.8%. During that year she was treated with folic acid, low-dose aspirin and allopurinol and did not receive regular blood transfusions.

For the leg ulcer, different local therapies were used including antibiotics, hyperbaric oxygen therapy, skin autologous graft transplant and local applications of macrophage suspension. In addition to the local treatment, systemic therapeutic options were employed including systemic antibiotics and antimicrobial therapy as well as systemic hyperbaric oxygen therapy that was administered in a hyperbaric

chamber. There was no improvement in her condition.

Between the ages of 20 and 29 the patient underwent different therapeutic approaches including oral hydroxyurea, regular blood transfusions every 3 weeks, combined therapy of oral hydroxyurea and regular blood transfusions or sporadic on-demand transfusions. Only transient and incomplete healing of the ulcer was achieved.

At age 29 a new blood transfusion regimen of one unit of packed red cells every 3 weeks was started, in addition to hydroxyurea therapy and desferrioxamine. During that year the pre-transfusion mean hemoglobin level was 7.9 g/dl and HbF 48%. No clinical improvement was seen. At age 32, the blood transfusion regimen was increased to two units of packed red cells every 3 weeks with the patient still receiving hydroxyurea and desferrioxamine. The pre-transfusion mean hemoglobin level was 9 g/dl, HbF 23% and hemoglobin A 63%. Towards the end of the second year of this protocol the leg ulcer was completely healed, and there was no recurrence for more than 2 years of follow-up with the same treatment.

COMMENT

Leg ulcers are a common complication of thalassemia intermedia, occurring in as much as one-third of patients with untreated or poorly controlled disease. They usually appear in the second decade of life and are generally located on the medial

HbF = fetal hemoglobin

Leg ulcer in the internal malleoli



or lateral malleoli. The ulcers emerge after a minor trauma and tend to expand rapidly [1]. They are slow to heal and tend to recur or become chronic, causing severe pain, disability and esthetic problems that are difficult to manage for both patients and physicians.

The etiology of thalassemic leg ulcers seems to be multifactorial with the main pathogenic mechanism appearing to be tissue hypoxia secondary to the anemia and the high affinity of fetal hemoglobin for oxygen, since fetal hemoglobin causes shifts in the hemoglobin-oxygen dissociation curve toward higher oxygen affinity, resulting in tissue hypoxia [3]. The percentage of HbF in thalassemia intermedia patients varies greatly, ranging from 5% to almost 100% depending on whether the genotype is β^+ or β^0 thalassemia.

Others factors contributing to ulcer formation include: a) abnormal rheological behavior of the diseased erythrocytes characterized by increased rigidity of their cellular membrane and enhanced adherence to endothelial cells, b) local edema due to venous stasis and possibly right heart insufficiency, c) repetitive local trauma and skin infections, and d) hypercoagulability and prothrombotic tendency [2].

The presence of hypercoagulability in thalassemia patients is well known. Several etiologic factors may play a role in the pathogenesis. The specific changes in the lipid membrane composition of the abnormal red blood cells and the hemosiderosis may contribute to activation of the coagulation process and activation of other blood cells, including platelets, monocytes and granulocytes, alone or together, which may induce activation of the vascular endothelium, further contributing to the thrombotic process [4].

Reduced levels of natural anticoagulant proteins were also reported in thalassemia patients, while a higher incidence of thromboembolic events was reported in thalassemia intermedia patients. Venous thrombosis is more prevalent in patients who do not receive regular transfusions and who have undergone splenectomy.

Those patients may be more susceptible to thromboembolism because they have more circulating damaged red blood cells and increased platelet counts [4].

Hypercoagulable disorders may contribute to the development and poor healing of leg ulcerations, either indirectly as a consequence of venous thrombosis, or directly by thrombus formation in small arteries, arterioles, capillaries or venules. A recent study reports that in a cohort of 30 patients with chronic leg ulcers 70% were associated with one or more thrombophilic factors [2]. Prothrombotic states and antiphospholipid antibodies are thought to contribute to vasculopathy and leg ulcers in patients with connective tissue diseases [5]. Successful treatment with anticoagulants was reported in some cases.

The treatment of leg ulcers in thalassemia is based on various conventional local measures such as banding, bed rest, avoidance of trauma and venous congestion, local hygienic precautions, antiseptic dressings, and local or systemic antibiotics. Other proposed measures are local administration of hyperbaric oxygen, topical synthetics, cellular matrixes, topical platelet-derived factors, skin grafting, local injections of granulocyte-macrophage colony-stimulating factor, and topical macrophage applications. Systemic treatments include oral administration of pentoxifylline in order to improve the blood flow and relieve the venous and lymphatic outflow. Treatment with high doses of ascorbic acid was also described. Healing of leg ulcers in thalassemia intermedia patients after oral administration of hydroxyurea was also reported and is likely due to improved rheological conditions of thalassemic red blood cells and their reduced adhesion to the vascular endothelium.

In thalassemia patients hydroxyurea therapy raises the total hemoglobin levels by raising HbF; the amelioration of the anemia is reflected in the clinical benefits reported [3]. The effect of hydroxyurea on the thalassemic red blood cells is not completely understood. The basic hypothesis is that the increase in the gamma

globin chain synthesis alleviates the β/α globin chain imbalance and decreases the damage produced by the excess of alpha-chains that precipitate in the red blood cells. The subsequent effect is an improvement in red blood cell morphology. Previous studies show that low doses of hydroxyurea increase the HbF content in erythroid cells with a consecutive increment in total hemoglobin. The final effect of hydroxyurea in thalassemic patients can then be related to an improvement in red blood cell survival.

Exchange blood transfusions have been reported to be successful in treating leg ulcers in a patient with high hemoglobin levels and high percentage of HbF. Increasing the total hemoglobin level with blood transfusions is one of the most feasible treatments of leg ulcers in thalassemia patients.

The patient presented here experienced less fatigue and had a general feeling of well-being on hydroxyurea therapy. An additional benefit is reduction of the erythropoietic activity that inhibits the expansion of the bone marrow and extramedullary erythropoiesis. Clearly, the successful treatment of any leg ulcer depends on an accurate diagnosis of the underlying etiology. Unfortunately, healing of chronic leg ulcers is not assured despite our understanding of the etiology and often requires time and persistence to find the appropriate therapy for each patient. The case reported here of a thalassemia intermedia patient with a non-healing chronic leg ulcer, present for more than 14 years despite several different local and systemic therapeutic modalities, represents a significant therapeutic challenge. We believe that the hypercoagulability status of this patient, which included β -thalassemia intermedia, heterozygosity for factor V Leiden and thrombocytosis, may contribute to the formation and perpetuation of the leg ulcer that was resistant to most of the treatments. Even the low-dose aspirin treatment that was indicated to prevent thrombotic complications due to thrombocytosis did not prevent development of the ulcer. A

successful response was obtained only after the combination therapy of intensive blood transfusions combined with hydroxyurea. Only following an increase in mean pre-transfusional hemoglobin levels above 9 and a reduction of fetal hemoglobin below 25% was improvement of peripheral tissue oxygenation achieved, followed by complete healing of the ulcer. Another beneficial role of regular blood transfusions combined with hydroxyurea therapy is the reduction of circulating abnormal red blood cells and amelioration of the hypercoagulable state.

Screening for thrombophilia should be considered in any patient with hemoglobinopathies and leg ulcers. The use of anticoagulant therapy in those cases warrants further investigation since only case reports have been published, not control-based studies.

Corresponding author:

Dr. C. Levin

Pediatric Hematology Unit, HaEmek Medical Center, Afula 18101, Israel

Phone: (972-4) 649-4189

Fax: (972-4) 649-5589

email: levin_c@cclalit.org.il

References

1. Gimmon Z, Wexler MR, Rachmilewitz EA. Juvenile leg ulceration in beta-thalassemia major and intermedia. *Plast Reconstr Surg* 1982; 69: 320-5.
2. Brandt HR, de Lorenzo Messina MC, Hirayama JT, et al. Prevalence of thrombophilia associated with leg ulcers. *Br J Dermatol* 2009; 160: 202-3.
3. Galanello R, Barella S, Turco MP, et al. Serum erythropoietin and erythropoiesis in high- and low-fetal hemoglobin beta-thalassemia intermedia patients. *Blood* 1994; 83: 561-5.
4. Eldor A, Rachmilewitz EA. The hypercoagulable state in thalassemia. *Blood* 2002; 99: 36-43.
5. Shanmugam VK, Steen VD, Cupps TR. Lower extremity ulcers in connective tissue disease. *IMAJ Isr Med Assoc J* 2008; 10: 534-6.

Capsule

TB drug tolerance exposed

One of the reasons tuberculosis (TB) continues to be a substantial public health problem is because the bacteria that cause TB, *Mycobacterium tuberculosis*, develop drug tolerance quickly. This requires patients to follow a 6-month drug regimen to ensure bacterial eradication, to which many patients fail to adhere. In order to identify new drug targets that may lead to shorter therapeutic regimens, Adams et al. dissected the development of drug tolerance in a zebrafish model of TB. Zebrafish infection with *Mycobacterium marinum* followed a similar disease course as human infection, which included the rapid development of drug tolerance. Multidrug-tolerant bacteria

were present in macrophages just days after infection and were expanded and disseminated by granulomas. Bacteria acquired tolerance by replicating in macrophages, in both fish and mammalian cells. Upon infection, macrophages increased expression of bacterial efflux pumps, which can pump drugs out. Use of pump inhibitors demonstrated that these complexes mediated drug tolerance. Together, these studies suggest that adding efflux pump inhibitors to the standard TB therapies may be an effective way to reduce the course of treatment.

Cell 2011; 145: 1

Eitan Israeli

Capsule

Progranulin protects against rheumatoid arthritis

Rheumatoid arthritis is a systemic autoimmune disease that principally affects synovial joints, including knee, finger, hip and wrist. The inflammatory cytokine tumor necrosis factor-alpha (TNF α) contributes to disease pathogenesis, and targeted therapies against TNF α are currently in use. Because the therapeutic efficacy and side effects of anti-TNF α treatments differ among patients, there is interest in discovering new therapies. Tang et al. report that the growth factor progranulin may represent a potential therapeutic target in the treatment of rheumatoid arthritis. Progranulin

binds directly to TNF receptors 1 and 2 and competes with TNF α for receptor binding. Progranulin deficiency protected against the development of inflammatory arthritis in multiple mouse models of the disease. Furthermore, an engineered protein composed of peptide fragments of progranulin retained TNF receptor binding prevented the development of inflammatory arthritis in mouse models, and decreased the mouse disease symptoms when used therapeutically.

Science 2011; 331: 478

Eitan Israeli

“I don't know anything about music. In my line you don't have to”

Elvis Presley (1935-1970), American rock'n roll singer and cultural icon of the 20th century. Incorporating country, rhythm, blues and gospel, Elvis was one of the best selling solo artists. His uninhibited performance style made him enormously popular – and controversial. His abuse of prescription drugs led to his untimely death at age 42. His home “Graceland” continues to be a site of pilgrimage for millions

Melanosis Enteri Discovered on Capsule Endoscopy of the Small Bowel

Yaron Niv MD FACG AGAF

Department of Gastroenterology, Rabin Medical Center (Beilinson Campus), Petah Tikva, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

KEY WORDS: melanosis, pseudomelanosis, capsule endoscopy, small bowel

IMAJ 2011; 13: 319–320

Melanosis in the colon was described as a brownish discoloration of the mucosa caused by the accumulation of pigment in macrophages within the lamina propria. The pigment was initially thought to be melanin or a melanin-like substance. Subsequently, the pigment proved to be lipofuscin, both histochemically and ultra-structurally [1]. There is a strong association between melanosis coli and chronic use of anthraquinone laxatives, and a cause and effect was established in laboratory animals [2]. Melanosis develops in more than 70% of people after chronic use of anthraquinone laxatives (cascara sagrada, aloe, senna, rhubarb, frangula). The condition is reversible, and the pigment disappears within one year of discontinuing the laxatives. The pigment lies within macrophages that swallowed damaged epithelial cells; epithelial abnormalities were found on electron microscopy [3].

A relationship between melanosis coli and the development of colorectal cancer was suspected but not confirmed in a prospective case-control study [4]. Other confounding factors might be involved in the increased risk of colorectal cancer suggested by earlier studies.

Colonic polyps and cancer lack pigment-containing macrophages and are therefore easy to find during colonoscopy in patients with melanosis coli. The pigment is more intense in the right colon compared to the distal colon, probably

due to the higher luminal concentration of the pigment and the difference in absorption capacity and macrophage population along the colon [5]. This phenomenon raises the question why melanosis is so rare in the small intestine. Is the absorption of lipofuscin unique to the colon and is the pigment excluded by the small bowel mucosa? The terminal ileum is accessible on colonoscopy, and pigmentation of the terminal ileum should not be missed. It is expected that the terminal ileum will be pigmented heavily while the colon is involved in melanosis coli, but this is not true.

We describe a case of extensive melanosis of the small bowel in a woman with melanosis coli as first demonstrated by capsule endoscopy.

PATIENT DESCRIPTION

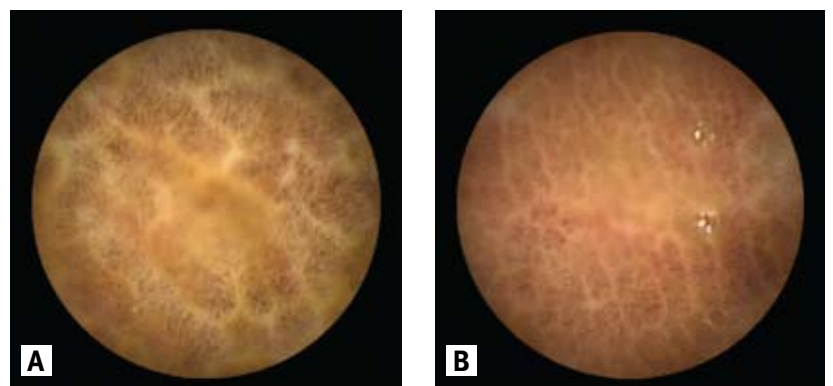
A 79 year old woman was admitted for evaluation with capsule endoscopy of iron deficiency anemia and positive fecal occult blood test. Before examination her trans-

ferrin, iron and ferritin levels were normal because she was on chronic iron therapy. On admission her hemoglobin was 7.2 g/dl which rose to 10.6 g/dl after blood transfusion. Iron therapy was discontinued a week before capsule endoscopy.

Her medical history disclosed ischemic heart disease, acute myocardial infarction, transient ischemic attack, chronic renal failure, cholelithiasis, hypothyroidism and chronic constipation, and she had undergone carotid endarterectomy. Her medications included aspirin, omeprazole, nifedipine, amiloride hydrochloride, simvastatin, furosemide and isosorbide mononitrate. She had been taking various types of laxatives for the last 20 years.

A month before the capsule endoscopy she underwent gastroscopy and colonoscopy, which demonstrated normal upper gastrointestinal tract but severe melanosis coli. Capsule endoscopy revealed severe extensive melanosis along the small bowel, starting in the proximal jejunum and reaching the terminal ileum [Figures A and B]. Partial villous atrophy was

Melanosis enteri – pigmentation of **[A]** the proximal jejunum and **[B]** proximal ileum in a patient with melanosis coli



also noted in the same areas of the small bowel.

Further investigation included blood carotene level, xylose absorption test and quantitative stool collection for fat; all were normal. Vitamin B12 level was 695 pmol/L (normal 138–781). The patient was followed for 8 years until her death at age 87.

COMMENT

The pigment in melanosis coli is localized within the colon as there is usually no pigment deposition in the small intestine. Anthraquinone laxatives cause damage to the colonocytes; the damaged organelles are sequestered in the autolysosomes of macrophages and result in lipofuscin bodies. Since the small bowel, especially the terminal ileum, is rich in macrophages, there is no reasonable explanation for small bowel sparing by this process. It is possible that the rich microbial flora in the colon is responsible for the difference. Another explanation may be the structural difference between colonocytes and

enterocytes, which have villi and a more developed brush border.

To the best of our knowledge this is the first report of an extensive distribution of small bowel pigmentation in a woman with melanosis coli, as demonstrated by capsule endoscopy. Our patient underwent capsule endoscopy for investigation of iron deficiency anemia and positive fecal occult blood test. The intense brown pigmentation, starting in the proximal jejunum and reaching the terminal ileum, was very similar to the pigmentation along the colon; thus the same pathophysiology is assumed. The effect of a massive pigment sequestration in the small bowel on absorption of food constituents, vitamins, minerals, water and electrolytes is not known. Because the small intestine is responsible for normal food absorption, in contrast to the limited ability and importance of the colon in this regard, melanosis enteri may have a substantial effect on the health status of the patient.

Since visualization of the small bowel by capsule endoscopy and double bal-

loon enteroscopy became common practice, we believe that additional cases of melanosis enteri will be diagnosed and characterized. In these cases the nature and outcome of melanosis enteri should be investigated.

Corresponding author:

Dr. Y. Niv

Dept. of Gastroenterology, Rabin Medical Center (Beilinson Campus), Petah Tikva 49100, Israel

Phone: (972-3) 937-7237

Fax: (972-3) 921-0313

email: nivyaron@013.net.il

References

1. Benavides SR, Morgante PE, Monserrat AJ, et al. The pigment of melanosis coli: a lectin histochemical study. *Gastrointest Endosc* 1997; 46: 131-8.
2. Walker NI, Bennett RE, Axelson RA. Melanosis coli: a consequence of anthraquinone-induced apoptosis of colonic epithelial cells. *Am J Pathol* 1988; 131: 465-76.
3. Balazs M. Melanosis coli: ultrastructural study in 45 patients. *Dis Colon Rectum* 1986; 29: 839-44.
4. Nusko G, Schneider B, Wittekind C, Hahn EG. Anthranoid laxative use is not a risk factor for colorectal neoplasia: results of a prospective case control study. *Gut* 2000; 46: 651-5.
5. Freeman HJ. "Melanosis" in the small and large intestine. *World J Gastroenterol* 2008; 14: 4296-9.

Capsule

Osteocalcin has important physiological roles in coordinating energy metabolism, bone remodeling and reproductive function

In females, the interaction between the reproductive system and bone physiology is well established: Loss of estrogen during aging is a causative factor in osteoporosis. Oury et al. describe a bone-reproductive system connection in males, where osteocalcin, a hormone produced in bone cells, controls the production of testosterone in the testes. Mice deficient in osteocalcin had smaller testes, decreased concentrations of blood testosterone, and reduced fertility. In the testes, osteocalcin increased expression of genes that participate in testosterone biosynthesis and spermatogenesis and inhibited stem cell death. Osteocalcin probably functions by binding the

G protein-coupled receptor Gprc6a, which is specifically expressed in Leydig cells of the testes. Direct binding of osteocalcin to Gprc6a was not directly demonstrated, but mice with reduced expression of Gprc6a in Leydig cells showed impaired testicular function similar to that in osteocalcin-deficient mice. Osteocalcin, which also regulates metabolism through effects on pancreatic beta cells and fat cells, thus appears to have important physiological roles in coordinating energy metabolism, bone remodeling and reproductive function.

Cell 2011; 144: 796

Eitan Israeli

“Always forgive your enemies, but never forget their names”

John F. Kennedy (1917-1963), 35th U.S. president who continues to rank highly in public opinion ratings of former American presidents. Events during his presidency included the Bay of Pigs invasion, the Cuban missile crisis, the space race, the building of the Berlin Wall, and the African American Civil Rights movement.

“A meeting is an event where minutes are taken and hours wasted”

Anonymous

Metastatic Breast Cancer Imitating Acute Diverticulitis

Ilana Haas Hamish MD¹, Haim Paran MD¹, David Cohen MD² and Mordechai Gutman MD¹

¹Department of Surgery B, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

²Department of Surgical Pathology, Herzliya Medical Center, Herzliya, Israel

KEY WORDS: metastatic breast cancer, gastrointestinal tract, infiltrating lobular carcinoma, diverticulitis

IMAJ 2011; 13: 321–322

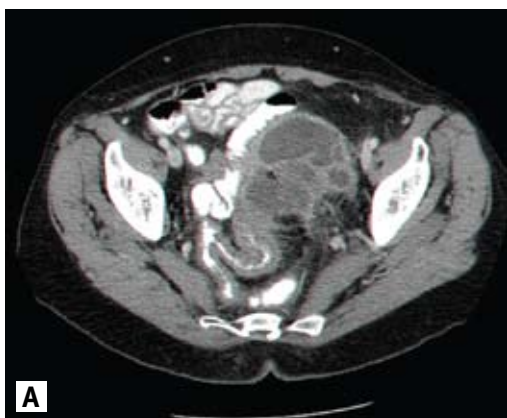
Carcinoma of the breast has the potential for widespread dissemination but metastases to the gastrointestinal tract are infrequent. Although rare, metastatic spread to the intestinal tract occurs mainly in infiltrating lobular carcinoma [1] and present late in the course of the disease, usually after an average of 9.5 years but sometimes as long as 20 years after the initial diagnosis [2]. This long interval usually results in delayed diagnosis. We present a patient with metastatic infiltrating lobular carcinoma in the sigmoid colon 16 years after being treated for an infiltrating lobular carcinoma of the breast. The presenting clinical picture was of acute diverticulitis, and the correct diagnosis was made only at the operation.

PATIENT DESCRIPTION

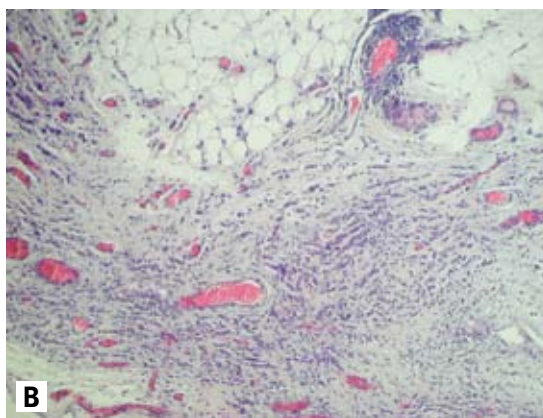
A 63 year old woman underwent a lumpectomy and axillary dissection at the age of 49 due to infiltrating lobular carcinoma of the left breast (Stage T-2, N-0). She was subsequently treated with radiation but not chemotherapy, and then followed yearly with no signs of recurrence. She was admitted urgently to the department of surgery due to left lower-quadrant abdominal pain. On examination she had focal tenderness in the left lower quadrant. An abdominal computed tomography scan showed an inflammatory process involving the sigmoid colon with a peri-colonic abscess consistent with sigmoid diverticulitis [Figure A]. She was treated with broad-spectrum antibiotics and the abscess was drained percutaneously. Her condition improved and she was discharged from the hospital with oral antibiotics.

A follow-up CT scan 3 weeks later showed significant regression of the inflammatory process. Despite the radiological improvement the patient remained symptomatic with abdominal discomfort and

constipation. A colonoscopy demonstrated a narrowing of the lumen that did not allow passage of the instrument but did not show any pathology in the mucosa. She was then referred for a virtual colonoscopy that also showed a narrowing of the sigmoid colon. Because of the ongoing abdominal symptoms and inability to rule out a tumor, surgical resection was contemplated. At surgery an inflammatory mass involving the sigmoid colon and the left adnexa was revealed. A sigmoidectomy and left salpingo-oophorectomy were performed. The postoperative course was uneventful. The histopathology examination of the specimen showed numerous diverticular outpouchings of the mucosa which were particularly prominent in the area of stenosis of the bowel lumen. The colon itself had a benign mucosa. Within the adipose tissue there were four small benign lymph nodes. In the same area of the serosal surface of the colon and within the fibroadipose connective tissue, deposits of foreign tissue were observed. Microscopic examination disclosed metastases of infiltrating lobular breast carcinoma [Figure B]. The tumor cells



A



B

[A] CT scan showing the inflammatory process involving the sigmoid colon and the abscess that was later drained percutaneously under CT guidance

[B] Cellular infiltrate just beneath the peritoneal surface showing "single file" pattern of uniform small tumor cells typical of lobular carcinoma of the breast

were Ca 15-3 positive, strongly positive to estrogen but negative to progesterone. Sixty percent of the tumor cells stained weakly for HER-2/neu. Following this finding the patient had a metastatic work-up that was negative. She is currently being treated with hormonal therapy.

COMMENT

Gastrointestinal metastases from breast carcinoma are very rare, occurring in only 0.8% of cases [3], usually from infiltrating lobular carcinoma. The clinical presentation can mimic Crohn's disease [4], colon cancer [3] and even diverticulitis [5].

In the present report we describe a patient with the clinical symptoms and findings consistent with complicated diverticulitis, 16 years after she was operated for an infiltrating lobular carcinoma. A CT scan and a colonoscopy were not diagnostic of the metastatic disease since

the metastases were only seen in the serosa and fibroadipose connective tissue surrounding the colon. The growth pattern was the same as seen in infiltrating lobular carcinoma. The long interval between the first presentation of the breast cancer and the metastatic disease was also misleading.

In conclusion, metastatic lobular breast cancer can occur in the gastrointestinal tract even after long periods. A high index of suspicion is needed because the diagnosis can be difficult and sometimes it is impossible to differentiate it from other gastrointestinal pathologies including inflammatory processes and primary colon cancer. Since hormonal and chemotherapy treatment are readily available and highly effective for the treatment of this type of cancer, prompt diagnosis is of utmost importance. Immunohistochemical markers can help in differentiating it from other malignant

tumors and in planning the adjuvant therapy.

Corresponding author:

Dr. M. Gutman

Dept. of Surgery B, Sheba Medical Center, Tel Hashomer 52621, Israel

Phone: (972-3) 530-8167, **Fax:** (972-3) 530-8157

email: Motti.Gutman@sheba.health.gov.il

References

1. Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. *Breast Cancer Res* 2004; 6 (3): R149-56.
2. Nazareno J, Taves D, Preiksaitis HG. Metastatic breast cancer to the gastrointestinal tract: a case series and review of the literature. *World J Gastroenterol* 2006; 12 (38): 6219-24.
3. Shimonov M, Rubin M. Metastatic breast tumors imitating primary colonic malignancies. *IMAJ Isr Med Assoc J* 2000; 2: 863-4.
4. Easter DW, Jamshidipour R, McQuad K. Laparoscopy to correctly diagnose and stage metastatic breast cancer mimicking Crohn's disease. *Surg Endosc* 1995; 9 (7): 820-3.
5. Defrawi T, Goyal A, Duan X, Kott M, Fischer CP, Adler DG. Breast cancer metastatic to the colon 20 years after bilateral mastectomy. *Endoscopy* 2006; 38E1.

Capsule

The Hh signaling pathway may be a possible therapeutic target for brain tumor

Brain cancer is the most common solid tumor in children. For children with medulloblastoma, survival rates have steadily improved as a result of optimized therapies. In contrast, children with an aggressive brainstem tumor called DIPG (diffuse intrinsic pontine glioma) are far less fortunate, with death occurring usually within a year. Because biopsy specimens of human DIPG are rare and because there are no relevant animal models, little is known about the cellular and molecular origins of these tumors. A study by Monje et al. provides insight into both the likely cell of origin of DIPG and a signaling pathway that may help promote tumor growth. The culprit cell appears to be a previously

uncharacterized neural precursor cell in the normal human brainstem. The density of these cells peaks during the time of childhood, when DIPGs most commonly arise. In a cell culture model, human DIPG cells showed activation of the Hedgehog (Hh) signaling pathway, which is critical to normal brain development and which is aberrantly activated in other human cancers, including medulloblastoma. Thus, DIPG probably arises through dysregulation of postnatal neurodevelopment, and the Hh signaling pathway may be a possible therapeutic target for this tumor.

Proc Natl Acad Sci USA 2011; 108: 4453

Eitan Israeli

“Kind words can be short and easy to speak, but their echoes are truly endless”

Mother Theresa (1919-1947), Albanian-born Catholic nun who founded the Missionaries of Charity in Calcutta. Her humanitarian work with the poor, the sick and the dying extended to 610 missions in 123 countries. She won the Nobel Peace Prize in 1979 and after her death was beatified by Pope John Paul II. Her legacy is not without controversy and she has been criticized for her strong stance against abortion and contraception and belief in the spiritual goodness of poverty

“Peace is not an absence of war, it is a virtue, a state of mind, a disposition for benevolence, confidence, justice”

Baruch Spinoza (1632-1677), Dutch Jewish philosopher today considered one of Western philosophy's most important thinkers. Although well versed in Jewish texts, he developed highly controversial ideas regarding the authenticity of the Hebrew Bible and the nature of the Divine, which it is believed led Jewish community leaders to excommunicate him