jejural biopsy obtained a few months after initiation of a gluten-free diet, were interpreted as normal.

Comment
Recent data indicate that an elevated plasma level of the thiol-containing amino acid homocysteine is a common, independent, easily modifiable and possibly causal risk factor for atherosclerosis, which may be no less important than hypertension, hypercholesterolemia or smoking [1].

Hyperhomocysteinemia has been associated with chronic renal failure, low plasma levels of vitamin co-factors (B6, B12 and folate), aging, menopause, and cardiac or kidney transplantation. Mutations in any of the three enzymes related to homocysteine metabolism - namely cystathionine-β-synthase, methylenetetrahydrofolate reductase, or methionine synthase - critically affect the eventual plasma level of that thiol-containing amino acid [2]. Studies both in vitro and in vivo point to several possible mechanisms of vascular damage mediated by high homocysteine levels. These include endothelial dysfunction, activation of factor V and tissue-type plasminogen activator, enhanced platelet aggregation, and inhibition of protein C.

Thromboembolic complications (deep vein thrombosis, stroke, cardiac thrombosis), though rare, have been described in chronic ulcerative colitis and Crohn’s disease [3]. These vascular complications have been attributed to hypercoagulation manifested by thrombocytosis, increased thromboplastin generation time, and increase in fibrinogen and clotting factor VIII. The literature contains few solid data on a possible link between celiac disease and thromboembolic events.

A Medline search revealed four reports: two from Switzerland and Norway describing an association between hyperhomocysteinemia and celiac disease, and two from Australia and France on deep venous thrombosis and splenic thrombosis (respectively) as the presenting feature of celiac disease and hereditary hyperhomocysteinemia [4,5].

The present report appears to be the first description in an English-language journal of a patient suffering from a possibly related combination of celiac disease with acquired folic acid deficiency due to malabsorption causing secondary hyperhomocysteinemia, cardiac thrombosis, coronary arteriosclerosis, carotid arteriosclerosis, and recurrent stroke. We suggest that future studies investigate vitamin status and homocysteine metabolism in celiac disease and other malabsorption syndromes.

References

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Leukemoid Reaction Associated with Transitional Cell Carcinoma

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Leukemoid reaction is an exaggerated myeloid response to several stimuli including infections, allergies, burns, intoxication, acute hemorrhage, and malignant neoplasms [1,2]. It is defined as a persistent neutrophilia of 3.000–50,000 cells/μl or greater. The term is used to distinguish this degree of neutrophilia from leukemia. In leukemoid reaction, neutrophils are usually mature and not clonally derived.

Carcinomas of colon, lung and kidney have been associated with leukemoid reaction as a paraneoplastic syndrome. This was attributed to the secretion of granulocyte colony-stimulating factor by the tumor, and was associated with aggressive tumor cell growth and a poor clinical outcome [1]. Leukemoid reaction has rarely been reported in patients with primary bladder cancer. We report a case of leukemoid reaction associated with transitional cell carcinoma of the urinary bladder. To our knowledge, this is the fifth case reported in the literature.

Patient Description
A 72 year old man was admitted for elective transurethral resection of a bladder tumor. He had a history of heavy smoking and glaucoma. Physical examination revealed...
right flank tenderness and a right pelvic firm fullness on rectal examination. Body temperature was normal. Laboratory analysis revealed leukocytosis with left shift (24,000/mm$^3$ 90% neutrophils) while other hematologic parameters were normal. Urine and blood culture showed no bacterial growth. Preoperative intravenous urography and sonography demonstrated right moderate ureterohydronephrosis and a large mass in the right wall of the urinary bladder.

The patient underwent incomplete transurethral resection of a bladder tumor because of the tumor size. Due to persistent ureterohydronephrosis a percutaneous nephrostomy was inserted. The patient was discharged in good physical condition with no fever, but with high leukocyte count (20,000/mm$^3$). The pathologic examination revealed high grade muscle-invasive (T2) transitional cell carcinoma. Elective radical cystectomy was scheduled. Two weeks later, the patient was admitted with high fever of 39°C and right flank pain, and parenteral antibiotic was initiated. Leukocyte count was 32,400/mm$^3$ (91% neutrophils). Blood smear showed marked leukocytosis with neutrophils but no immature forms. Three days after admission the fever resolved, but the leukocyte count was still high (33,000/mm$^3$, 92% neutrophils). Repeated blood and urine cultures were sterile. Chest X-ray and abdominal computed tomography showed no metastasis, abscess or other reasons for leukocytosis.

Radical cystectomy with ileal conduit was performed. Leukocyte count before the operation was high - 42,900/mm$^3$ (93% neutrophils), but 12 hours after the operation leukocyte count decreased to 14,500/mm$^3$. In subsequent blood counts 2 days and 1 week after surgery the leukocyte counts were 11,900/mm$^3$ and 10,900/mm$^3$, respectively. Two weeks after the operation, leukocyte count decreased to 9,000/mm$^3$.

Comment

Paraneoplastic syndrome is defined as hormonal, neurologic, hematologic and other clinical and biochemical disturbances associated with malignant neoplasms not directly related to invasion by the primary tumor or its metastases [2]. As many as 20% of all cancers may be associated with paraneoplastic syndromes caused by tumor secretion of hormone or cytokine-like substances [1].

A few paraneoplastic syndromes have been reported in patients with metastatic transitional cell carcinoma including hypercalcemia, thrombocytosis, eosinophilia, nephrotic syndrome, acanthosis nigricans, dermatomyositis, polymyositis, and leukemoid reaction [2].

Leukemoid reaction has rarely been reported in patients with primary bladder carcinomas. In a literature review we found only five cases of a leukemoid reaction in bladder cancer. All five cases were associated with aggressive tumor cell growth and unfavorable clinical outcome. Two patients had rapid local recurrence 6 weeks after surgery [1]. Distant liver metastases at initial presentation were present in another two patients [2, 3]. In one patient the tumor had already invaded the pelvic wall at the time of diagnosis [4]. The leukocyte count ranged from 34,700 to 76,000/mm$^3$.

Paraneoplastic leukocytosis associated with bladder carcinoma has been shown to result from autonomous production of G-CSF by the tumor [1, 3, 5]. As a consequence of this autonomous factor, the serum levels of this factor increase significantly and lead to marked leukocytosis [1].

Fever is an integral component of leukemoid reaction. In our patient, the source of the fever was unclear. All blood and urine cultures were sterile, and chest X-ray and abdominal CT were normal. In our case, even when the patient had no fever, marked leukocytosis persisted. A dramatic decrease in leukocyte counts was demonstrated after surgery. G-CSF level was not measured, and the diagnosis of paraneoplastic leukemoid reaction in our patient was reached on a clinical basis.

In our patient leukocytosis was present at the time of diagnosis of the primary tumor and in the absence of metastases, which is in contrast to other reports where leukocytosis appeared with recurrence of the neoplasm and in the presence of metastases [3].

Leukocytosis in a patient with advanced transitional cell carcinoma may represent leukemoid reaction due to paraneoplastic secretion of G-CSF. When no other source for leukocytosis can be found, leukemoid reaction may be suspected and may be resolved with surgery.

References


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*Happiness is salutary for the body, but it is sorrow that develops spiritual strength*

*Marcel Proust (1871-1922), French novelist and critic, in The Past Recaptured*