Definitive Endovascular Repair of a Brucellar Descending Thoracic Aortic Aneurysm

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Brucellosis is a zoonotic disease of global importance. It has a worldwide distribution and is endemic in most Middle Eastern countries [1]. *Brucella* species are gram-negative, facultative, intracellular coccobacilli. The primary etiological agent of brucellosis in the Middle East is *Brucella melitensis*, harbored mainly by sheep and goats. Humans are infected by ingestion of contaminated milk products, direct skin contact with infected animal tissue, and inhalation of infected aerosolized particles [1]. Brucellosis in humans is generally characterized by fever, malaise, arthralgias and weight loss, but can affect multiple organ systems. Aortic involvement, typically manifesting as an infected (mycotic) aortic aneurysm, is a rare complication of brucellosis [2].

The definitive treatment of mycotic aortic aneurysms (MAA) must include a combination of vascular surgical intervention and prolonged antibiotic therapy [2]. The gold standard for vascular repair is open surgery with resection of the aneurysm, local debridement, and revascularization by in situ reconstruction or extra-anatomic bypass [2,3]. However, emergent open surgical repair of MAA can be a technically challenging procedure with high morbidity and mortality rates [3]. Endovascular aneurysm repair (EVAR) has become an increasingly accepted and less invasive surgical approach for MAA, with lower surgical risk compared to conventional open repair [3]. Several reports on the use of EVAR for brucellosis-induced MAA have shown promising results, but long-term outcomes remain unknown [4]. Thus, the role of EVAR as a definitive therapeutic option for MAA has yet to be established. We report the successful long-term outcome of endovascular repair of a brucellar descending aortic aneurysm with thoracic EVAR (TEVAR).

PATIENT DESCRIPTION

A 69 year old Bedouin man from southern Israel presented to the emergency room with a month-long history of dysphagia, abdominal pain and weight loss. He reported coughing up blood several times before his admission. His medical background included previous treatment for transitional cell carcinoma of the bladder.

On admission he looked cachectic and had severe upper abdominal sensitivity upon palpation. His pulse rate was 106 beats/minute and his temperature was 36.9ºC. His blood count was normal except for mild leukocytosis (leukocytes 9.23 x 10^3/mm^3). Serum electrolytes and creatinine were normal. Chest X-ray revealed bilateral upper lobe infiltrates.

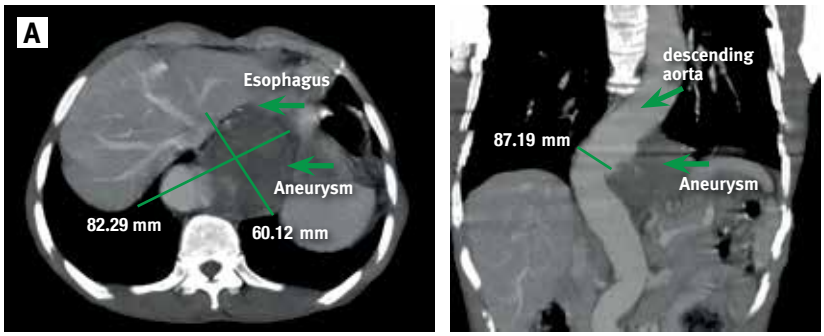
Three sputum and urine samples were negative for acid-fast bacilli. Cultures from these specimens were later reported as negative for *Mycobacteria*. Due to persistent upper abdominal pain, a gastroscopy was performed, and demonstrated an ulcerative lesion in the middle of the esophagus, as well as external compression of the distal esophagus. No active bleeding was seen during the procedure. A thoracoabdominal computed tomography (CT) scan was subsequently performed and showed an 82 mm diameter false aneurysm of the descending thoracic aorta [Figure 1A].

The patient was transferred to the department of Vascular Surgery where a temperature of 39.3ºC was recorded on the third day of admission. Blood cultures were drawn and empiric therapy with vancomycin and ciprofloxacin was initiated to cover nosocomial pathogens.

The following day, the patient remained febrile, with extremely labile blood pressure, and he developed recurrent vomiting. Imminent rupture of the MAA was suspected and the patient was taken to the operating room where an emergent endovascular implantation of an aortic graft was performed. The Valiant® Thoracic Stent Graft with the Captivia® Delivery System (Medtronic Vascular, Inc. Santa Rosa, CA, USA) was inserted by a transfemoral cut-down approach under local anesthesia. Completion angiography at the end of the procedure showed good stent graft position with no endoleak. There were no complications during or after the procedure.

On postoperative day 1, blood cultures were positive for *Brucella melitensis*. *Brucella* tube serum agglutination test showed titers of 1:80 for both Immunoglobulin M (IgM) and Immunoglobulin G (IgG). Vancomycin was discontinued and intravenous gentamicin was initiated together with doxycycline. Over the course of the hospital stay, the patient's general condition improved with remission of fever and abdominal pain. He was discharged on postoperative day 10 and

Figure 1. [A] Thoracoabdominal computed tomography with angiography showing an 82 mm false aneurysm of descending thoracic aorta (2011)



[B] Follow-up computed tomography with angiography showing near complete involution of the aneurysm and the coils of the stent graft (2014)

was prescribed oral doxycycline 100 mg twice a day for 1 year with a proton pump inhibitor. The patient attended the vascular surgery and infectious disease outpatient clinics annually, and underwent yearly radiological follow-up.

During follow-up visits the patient was asymptomatic. C-reactive protein tests and liver function tests were consistently within normal range. *Brucella* antibody titers 3 years after the procedure were IgG 1:20 and IgM 1:60. The last CT angiography, performed 3 years following the TEVAR, revealed good position of the stent graft and full involution of the aneurysm [Figure 1B]. Transthoracic echocardiogram (TTE) performed in the third year of follow-up ruled out valvular pathology.

COMMENT

Vascular brucellosis occurs when the bacteria infect abnormal cardiac and vascular tissue, such as atherosclerotic plaques [2]. Cardiovascular complications account for about 80% of brucellosis-associated deaths [1]. Brucellar aortic involvement is the most common endovascular complication. There may be considerable under-diagnosis and under-reporting of this complication since many countries with a high brucellosis burden do not have access to sophisticated imaging modalities [2]. Elderly patients can occasionally present without fever, even while bacteremic, necessitating a high index of suspicion.

In the reported case, the endoscopic finding suggested that the hemoptysis reported by the patient at admission was in fact hematemesis, implying a risk of ongoing ulceration of the esophageal wall by the brucellar MAA. The CT angiography allowed for accurate diagnosis of a life-threatening aneurysm. Although the gold standard for repair of an infected aortic aneurysm is open surgery, the surgical team opted for repair of the aneurysm using EVAR.

EVAR has become increasingly accepted as a less invasive treatment option for MAA because it avoids aortic clamping and reduces blood loss after MAA [3-5]. However, the use of stent grafts as definitive procedures for MAAs without removal of the infected tissue remains controversial. Data on the long-term outcomes of endovascular surgical approaches to repair brucellar MAA are scarce, possibly for the same reasons as under-diagnosis (i.e., the countries with increased burden of disease do not always have advanced and accessible vascular surgical capability). The favorable clinical and radiological outcome of this patient, more than 3 years following the TEVAR and 1 year of antibiotic therapy, adds to the growing body of knowledge supporting stent grafts as a definitive solution for brucellar aortic MAAs. This approach requires patient compliance and access to meticulous clinical and radiological follow-up, which is available in Israel at no charge to the patient.

Aortic involvement due to *Brucella melitensis* infection is usually associated with endocarditis and ensuing septic emboli of the aortic wall, or with contiguous spread secondary to vertebral osteomyelitis [2]. Transesophageal echo (TEE), which was not performed in this case at presentation, might have detected a vegetation not visualized by transthoracic echocardiography. Revisions of the CT performed on admission at the levels of the thoracic vertebrae ruled out spondylitis or discitis. Since the patient improved clinically, and since inflammatory parameters were consistently low at follow-up, TTE and not TEE was performed after 3 years, and interpreted as normal. The patient continues follow-up due to the theoretical risk of recurrence in the presence of a prosthetic graft.

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Capsule

Exploiting cancer metabolism

Cancer-specific cell surface proteins can be targeted for the delivery of therapeutic agents. However, specific proteins may not always be expressed by a tumor. Wang et al. overcame this challenge by designing sugars to selectively label cancer cells. Small-molecule sugars (azides) can be metabolized by enzymes that are highly expressed in some tumors, including colon and breast cancer cells. Metabolized azides labeled endogenous cell surface proteins in cultured cancer cells and tumor-bearing mice. The azide moiety on the labeled proteins was subsequently recognized by another molecule carrying a drug, which was taken up by the cancer cells. Tumor growth was reduced, and animal survival improved by 86%.

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Eitan Israeli

Capsule

Mtb faces sirtuin death

New therapies are needed to combat *Mycobacterium tuberculosis* (*Mtb*), which is a poster child for drug resistance. Cheng and colleagues reported that *Mtb* infection down-regulates sirtuin 1, an oxidized nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase, in myeloid cells in animal models and patients with active disease. Activating sirtuin 1 inhibited intracellular growth of *Mtb*. It also inhibited persistent inflammatory responses, which decreased lung pathology. Furthermore, sirtuin 1 activation enhanced the efficacy of a first-line anti-tuberculosis drug. These effects may have been due in part to myeloid cell modulation because mice with myeloid cell-specific sirtuin 1 deficiency had both increased inflammation and higher susceptibility to infection than wild-type controls. Thus, sirtuin 1 may be a target for host-directed therapy for *Mtb.*

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Capsule

Myeloid progenitor cluster formation drives emergency and leukemic myelopoiesis

Although many aspects of blood production are well understood, the spatial organization of myeloid differentiation in the bone marrow remains unknown. Herault and co-authors used imaging to track granulocyte/macrophage progenitor (GMP) behavior in mice during emergency and leukemic myelopoiesis. In the steady state, they found individual GMPs scattered throughout the bone marrow. During regeneration, they observed expanding GMP patches forming defined GMP clusters, which, in turn, locally differentiate into granulocytes. The timed release of important bone marrow niche signals (SCF, IL-1β, G-CSF, TGFβ and CXCL4) and activation of an inducible *Irf8* and β-catenin progenitor self-renewal network control the transient formation of regenerating GMP clusters. In leukemia, the authors showed, GMP clusters are constantly produced owing to persistent activation of the self-renewal network and a lack of termination cytokines that normally restore hematopoietic stem-cell quiescence. These results uncover a previously unrecognized dynamic behavior of GMPs *in situ*, which tunes emergency myelopoiesis and is hijacked in leukemia

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"A poor idea well written is more likely to be accepted than a good idea poorly written"

Isaac Asimov (1920-1992), American writer and professor of biochemistry at Boston University. He was known for his works of science fiction and popular science and was a prolific writer