

Multiple Sterile Splenic and Lymph Node Abscesses in a Patient with Long-Standing Ulcerative Colitis

Naseem Shadafny MD¹, Samuel N. Heyman MD¹, Michael Bursztyn MD¹, Anna Dinaburg MD², Ran Nir-Paz MD³ and Zvi Ackerman MD¹

Departments of ¹Medicine, ²Radiology and ³Microbiology & Infectious Diseases, Hadassah-Hebrew University Hospitals, Jerusalem, Israel

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Patients with inflammatory bowel disease (IBD) often present with a wide variety of pathological disorders that involve multiple non-intestinal organs and systems, such as the skin and oral mucosa, or musculoskeletal, hepatobiliary and ocular manifestations. Some of these extra-intestinal expressions reflect the inflammatory activity of the bowel disease, while others are unrelated to disease flare-ups. Recently we observed a patient with severe ulcerative colitis (UC) who suffered from multiple sterile visceral abscesses, a rarely reported and unrecognized extra-intestinal manifestation of IBD.

PATIENT DESCRIPTION

A 27 year old Jewish male of Georgian origin was hospitalized in April 2014 because

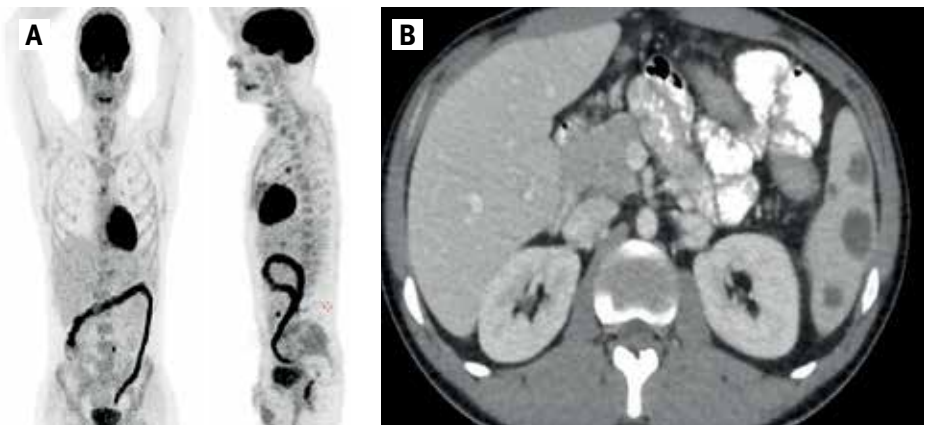
of fever andodynophagia. He was known to suffer from ulcerative pan-colitis since the age of 21 and was initially treated with steroids, followed by mesalamine and azathioprine. His disease course was characterized by alternating improvements and exacerbations, requiring ongoing steroid courses and without a full remission; at his best he had about six loose non-bloody bowel movements a day. Treatment with infliximab, initiated in 2012, was abandoned after three induction doses as it did not provide further improvement and because of repeated hospitalizations for the treatment of epididymitis (October 2012), amoebic dysentery caused by *Entamoeba histolytica* (January 2013), cytomegalovirus colitis (May 2013), and *Clostridium difficile* toxin-related colitis (September 2013).

In January 2014 the patient developed severe thyrotoxicosis due to Graves' disease that went into remission after treatment with mercaptizol. At the same time, in addition to long-standing repeated episodes of oral aphthosis, he developed a few ill-defined lesions at the nasal septum and alae nasi that resolved

spontaneously. In April 2014 he developed painful swallowing and fever (38°C) and increased levels of C-reactive protein (CRP). Computerized tomography (CT) disclosed a small para-esophageal collection and enlarged sub-carinal lymph nodes. Broad-spectrum antibiotic treatment with ceftriaxone was associated with a modest clinical improvement and only a partial resolution of the para-esophageal collection. Subsequent positron emission and computerized tomography (PET-CT) disclosed enhanced uptake of fluorodeoxyglucose in a lead pipe-like deformed colon and focal uptake in a few abdominal and mediastinal lymph nodes, including the para-esophageal node [Figure 1A]. Esophagogastroduodenoscopy was normal. An endoscopic ultrasound-guided biopsy from this lesion disclosed the presence of non-caseating granulomas. Staining for acid-fast organisms (Ziehl-Neelsen stain) and fungi (Silver stain) were negative, as were routine microbial cultures and 16S ribosomal RNA sequencing.

The patient responded to increasing doses of steroids with the disappearance

Figure 1. [A] Positron emission tomography (PET-CT) showing enhanced uptake by severely inflamed lead pipe-like scarred colon and in several para-esophageal, retropharyngeal and abdominal lymph nodes. The spleen is evidently intact. **[B]** Computerized tomography taken 3 weeks later, depicting multiple splenic abscesses



of odynophagia, but a week later erythema nodosum lesions appeared on the limbs, with morphologic features compatible with leukocytoclastic vasculitis. Increasing steroid dose resulted in gradual amelioration. However, 2 weeks later, at the end of May 2014, fever reappeared during gradual tapering of steroids, associated with left chest and left upper quadrant abdominal pain and rising indices of inflammation. Colonoscopy revealed the presence of macroscopic and microscopic severe pan-colitis.

Colonic infections were excluded by cultures and microscopic stool examination, and by stool polymerase chain reaction (PCR) for the *CDT B* gene. Tuberculosis, fungal and cytomegalovirus infections were ruled out by histology, specific cultures and PCR evaluation of the colonic mucosa obtained at colonoscopy. Repeated CT disclosed the presence of multiple splenic hypodense lesions (up to 2.6 cm), which were not present in the previous imaging, performed 3 and 6 weeks earlier [Figure 1B]. With the diagnosis of multiple splenic abscesses, one of these lesions was aspirated, revealing thick gray pus-like material that was negative for bacterial, mycobacterial and fungal agents. PCR for 16S ribosomal RNA was negative as well, as were repeated blood cultures. Trans-thoracic echocardiography and urinalysis were also unremarkable.

With the working hypothesis of sterile visceral abscesses associated with ulcerative colitis, the dose of prednisone was increased to 25 mg/day with prompt clinical resolution of symptoms within a few days. Repeated abdominal ultrasound studies confirmed gradual recovery of the splenic lesions as well, with a normal-appearing spleen 4 months later. In February 2015, after he finally consented, the patient underwent total colectomy, with an ileo-anal anastomosis and reconstruction of an ileal pouch. Since then he was weaned off steroids and has been symptom free for more than 18 months.

COMMENT

This case report illustrates a very unusual clinical course in a patient with protracted

unremitting severe refractory UC who developed sterile abscesses in the spleen and lymph nodes that responded to anti-inflammatory therapy.

The occurrence of such extra-intestinal manifestations of IBD has rarely been reported. In 2007 André and colleagues from the French Study Group on Aseptic Abscesses [1] reported a series of 30 patients who suffered from disseminated sterile visceral abscesses, 21 of them with IBD. This series, along with additional recent case reports [2-5], illustrate that necrobiotic nodules and sterile abscesses indeed might be considered as rare extra-intestinal manifestations of IBD.

In the report by Andrés et al. [1] the mean age at onset of sterile abscesses among IBD patients was 24, and the organs mostly affected by sterile abscesses were the spleen (15/21), followed by abdominal lymph nodes, liver and lung (13, 8 and 4/21 patients, respectively). Abscesses were also reported in muscles, peripheral lymph nodes, the pharynx, testis and even in the brain. In most patients more than one organ was involved, average 2.4 organs per patient [1]. Principal presenting symptoms were fever and abdominal pain (19 and 17 of 21 patients, respectively), and cutaneous or mucosal lesions were reported in 13/21 patients, all of which occurred in our patient. Our patient also fits well with this series, being young and displaying sterile abscesses in more than one organ, appearing in succession first in inflamed lymph nodes and subsequently in the spleen. It is tempting to assume that the epididymitis, reported in 2012, might have been a sterile abscess as well. He also presented with markedly elevated indices of inflammation, as did most patients in André's series [1].

Our patient developed sterile abscesses following a protracted course of unremitting UC. In contrast, in the cohort of patients presented by André's team, sterile abscesses often preceded or occurred concomitantly with the development of gastrointestinal manifestations (14/21), and their appearance in most cases did not reflect the activity of IBD, unlike other extra-intestinal

manifestations such as uveitis, arthritis or erythema nodosum. As with our patient, sterile abscesses were found to respond well to steroids, but relapse was common, occurring in 66% of patients [1].

Nine of the 19 IBD patients with sterile splenic abscesses reported by André et al. underwent diagnostic splenectomy. Conceivably this intervention is not needed today in comparable settings, taking into consideration the advanced diagnostic techniques to exclude infections that were used in our patient.

The pathogenesis of sterile abscesses in patients with IBD is obscure. Morphologically they are characterized by palisading histiocytes surrounding areas of central necrosis [1,4,5]. Additional inflammatory components may also be involved, such as vasculitis (resembling lesions of Behcet's disease or pyoderma gangrenosum) and dense infiltration of polymorphonuclear cells (also noted in pyoderma gangrenosum and in Sweet's syndrome). Testing for anti-neutrophilic cytoplasmic antibodies (ANCA) was positive in 4 of 18 patients with sterile abscesses associated with IBD, suggesting also a role for autoantibodies and complement binding in this disorder [1]. André et al. proposed that components of the immune system might be activated in IBD patients following the interruption of the intestinal mucosal barrier, leading to intense inflammatory response in distal organs, such as the spleen, liver or lymph nodes. They further suggested that marked neutrophilic infiltration may be mediated by interleukins released from histiocytes and lymphomononuclear cells, underscoring a possible clinical and pathophysiologic overlap with other autoinflammatory disorders, such as neutrophilic dermatoses, chronic recurrent multifocal osteomyelitis and Behcet syndrome [1].

In addition to their 30 original patients, André et al. [1] traced 19 other previously described case reports of visceral necrobiotic lesions and sterile abscesses, mostly associated with IBD, and a few more case records have been reported in the last few years [2-4]. It is conceivable that these rare manifestations are misdiagnosed and

under-reported, and their association with IBD may be overlooked [5].

As illustrated in our patient, sterile abscesses in IBD are steroid-responsive. A few reported patients were successfully managed with anti-tumor necrosis factor (TNF) antibodies, such as infliximab [1,2,5], underscoring its role in this disorder. However, previous ineffectiveness in the control of IBD with the flare-up of cytomegalovirus colitis excluded this option in our patient. To our knowledge, this is the first report to suggest colectomy for maintaining remission in aseptic systemic abscesses complicating UC.

In summary, the presence of visceral aseptic abscesses, particularly splenic lesions, should be added to the extended list of extra-intestinal manifestations of IBD. This might guide the diagnostic approach in similar cases, avoiding unnecessary surgical interventions and the frustrating futile treatment with various anti-infective agents.

Correspondence

Dr. S.N. Heyman

Dept. of Medicine, Hadassah-Hebrew University Medical Center, Mount Scopus Campus, Jerusalem 91240, Israel

Phone: (972-2) 584-4111

Fax: (972-2) 582 3515

email: Heyman@cc.huji.ac.il

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