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Case report

Vaginal sarcoidosis without other organ involvement in a patient with a history of endometrial cancer: A case report

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1. Introduction

Granulomatous inflammation is a histologic pattern containing histiocytes, or activated macrophages, that can be seen in tissues following cell injury. Its differential diagnosis is broad and includes infectious, autoimmune, toxic, allergic, and neoplastic conditions (Shah et al., 2017). Sarcoidosis is a systemic granulomatous disease that can affect any organ. Pulmonary and hilar lymph node involvement is by far the most common manifestation, present in 90% of cases, but other sites, including the skin, eye, liver, heart, and peripheral lymph nodes, may also be involved in 10–30% of cases (Judson, 2015). The female genital tract is the most rarely involved at < 1% of cases (Rosenfeld et al., 1989). The first vulvar sarcoidosis case was reported in 1985 (Tatnall et al., 1985), and most subsequent case reports have described uterine or vulvar involvement. To date, only a handful of vaginal sarcoidosis case reports have been published, primarily in association with other organ involvement (Allen and Judson, 2010; Xu et al., 2012; Schol et al., 2013; Sahin et al., 2016). A confounding factor in this particular case, which differentiates it from that which has been previously reported (Bakali et al., 2012), is that the patient has a history of endometrial cancer.

2. Case report

A 60-year-old woman presented to the gynecologic oncology clinic with a one-month history of markedly increased mucus vaginal discharge. She had a history of stage IIIA grade 1 endometrial adenocarcinoma status post TAH/BSO, omentectomy, and bilateral pelvic and para-aortic lymph node dissection followed by 6 cycles of chemotherapy (Carbo/Taxol) and had been in remission for the past eight years. She had a normal pelvic exam two months prior to this presentation. Her past medical and surgical histories are otherwise unremarkable. Physical exam demonstrated copious brown/mucus discharge and vaginal circumferential thickening with a more pronounced 2 × 3 cm area of thickening in the rectovaginal septum. Given concern for cancer recurrence, the patient underwent a vaginal biopsy and pelvic MRI. CA-125 level, which was elevated at 182 U/mL at time of cancer diagnosis, was normal at 10 U/mL.

The biopsy specimen exhibited non-necrotizing granulomatous inflammation and neither acid fast bacilli (AFB) nor fungal organisms were identified on AFB and Gomori methenamine silver stains, respectively (Fig. 1). In addition, the patient had no history of fever, cough, night sweats, new exposures, or GI symptoms and she had a normal colonoscopy one year prior to initial presentation. Pelvic MRI showed concentric thickening of the anterior and posterior vaginal walls but no discrete mass effect (Fig. 2A) and this was not consistent with a cancer recurrence. Dermatology and rheumatology were also consulted to help guide further work up and a chest radiograph, antinuclear antibody (ANA), rapid plasma reagin (RPR), C-reactive protein (CRP), and Prometheus inflammatory bowel disease (IBD) panel were all negative/normal.

After initial workup was negative for other etiologies, the lesion was treated as an inflammatory process with a methylprednisolone taper, which resulted in moderate symptomatic improvement, especially with the discharge. However, her symptoms returned after completion of the steroid taper and she was therefore started on dexamethasone 4 mg BID, weaned to 2 mg daily, along with vaginal triamcinolone. This medication regimen resulted in marked improvement on physical exam

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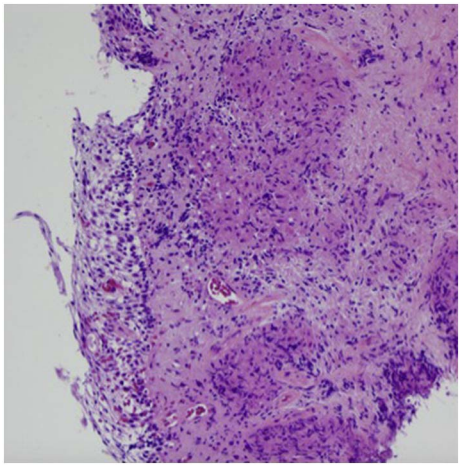

Fig. 1. Vaginal Biopsy Demonstrating Noncaseating Granulomatous Inflammation. A biopsy of the clinically and radiologically appreciated vaginal wall thickening shows noncaseating granulomatous inflammation of the vaginal lamina propria comprised predominantly of epithelioid histiocytes and lymphocytes. Examination of Grocott's methenamine silver (GMS) and acid-fast bacilli (AFB) staining revealed no microorganisms. No refractile foreign material was identified upon examination under polarized light (× 10).

and resumption of sexual activity. Due to atrophy, vaginal estrogen was added and the patient was eventually completely weaned off oral steroids four months after her initial presentation. She has since remained stable with respect to symptoms and physical exam on QOD vaginal steroids alternating with estrogen. On her most recent follow up, the discharge had improved and physical exam showed near resolution of rectovaginal thickening and stable anterior vaginal wall thickening. Repeat MRI showed interval near complete resolution of previously seen enhancement abnormalities within the vagina (Fig. 2B).

3. Discussion

In this case of a patient with a history of endometrial cancer presenting with a new vaginal mass shown to contain granulomatous inflammation on pathologic review, there are many etiologies to consider. Although vaginal sarcoidosis is our leading diagnosis in this case, the pathologic findings are not specific and the differential diagnosis for non-necrotizing granulomatous inflammation includes a number of other possibilities, including infections, other inflammatory/autoimmune processes, toxins, drug reactions, and neoplasms ("sarcoid-like" reactions). Refer to Table 1 for a list of specific etiologies within each category.

Some of the more common infectious etiologies to consider include coccidiomycosis (Chen et al., 1993), lymphogranuloma inguinale (Sami and Baloch, 2005), and tuberculosis (Ferrara et al., 1999). These are less likely in our case, given the lack of bacteria and fungal organisms with appropriate staining, and there were no findings on chest radiograph to support existence of a tuberculosis or fungal infection. Additionally, RPR was negative, ruling out syphilis. Of the inflammatory/autoimmune causes of non-necrotizing granulomas, Crohn's disease and lupus are the two of the more common ones after sarcoidosis. Crohn's disease was excluded given her lack of suggestive symptoms, a normal colonoscopy one year prior, normal CRP (< 0.1 mg/dL), and a negative IBD panel. Lupus was essentially ruled out, as the patient's ANA, a very sensitive marker for the disease, was normal. To address toxic and drug exposures, we relied on history from the patient; she denied any new environmental exposures and any new products or medications, specifically antibiotics and methotrexate. A normal blood count and lack of any other systemic symptoms put hematologic malignancies low on our differential diagnosis. Given her negative workup, many of the

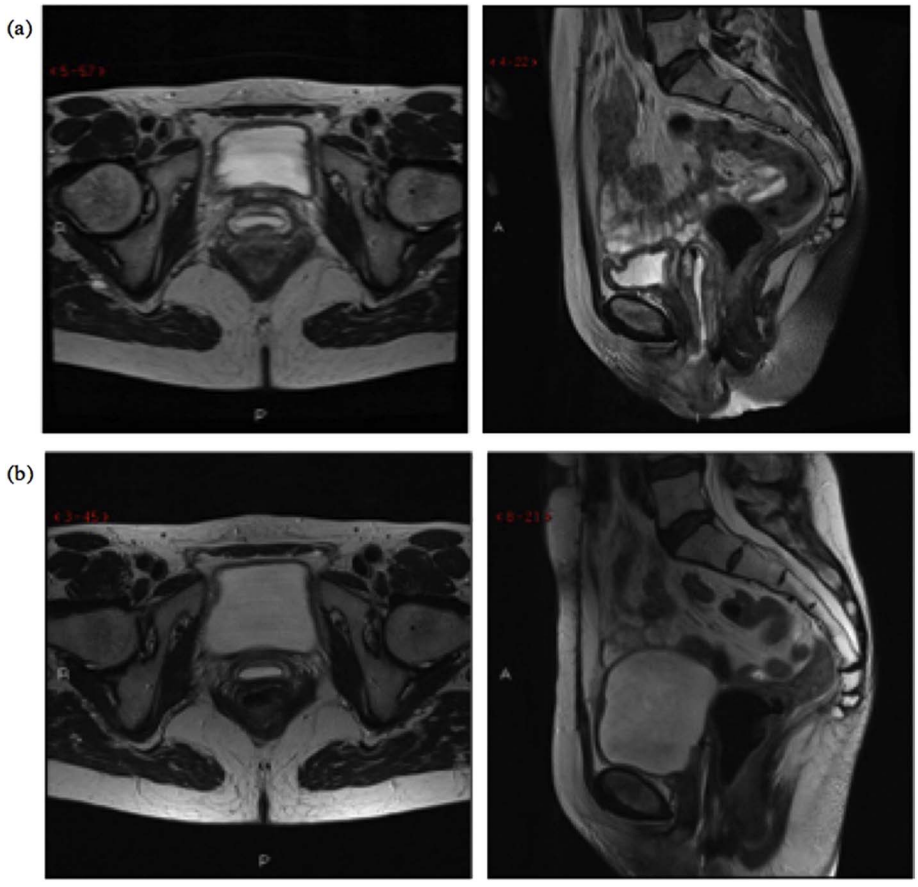

Fig. 2. Pelvic MRI Before and After Steroid Treatment. (a) T2-weighted MR images demonstrating hypointense non-mass like change in signal intensity in the posterior vaginal wall measuring 1.6 × 0.7 cm with avid post-contrast enhancement (axial image) and hypointensity measuring 1.1 × 0.6 cm in the anterior vaginal wall (sagittal image). There is no restriction of diffusion and no convincing evidence of recurrent tumor in the vagina or pelvis. (b) Axial and sagittal T2-weighted MR images showing near complete resolution of the two foci of abnormal enhancement seen on the previous MRI (a) eight months prior.

Table 1
Differential diagnosis for non-caseating granulomatous inflammation and workup.

Etiology	Examples	Key elements of workup
Infectious	*Candida* *Coxiella burnetii* Cytomegalovirus *M. tuberculous* Non-tuberculous mycobacteria	• Chest x-ray • Biopsy with Acid-Fast Bacilli and Gomori methenamine silver stains
	Lymphogranuloma inguinale Coccidiomycosis *Schistosoma*	• Hepatitis serology if clinical risk factors
	Toxoplasma gondii *Rickettsia* *Salmonella typhi* Hepatitis A & C viruses Syphilis	• Rapid plasma reagin
Autoimmune	Sarcoidosis Churg Strauss Giant cell arteritis Lupus	• Labs: C-reactive protein, erythrocyte sedimentation rate, angiotensin converting enzyme, serum calcium
	Crohn's disease Primary biliary cirrhosis Orofacial granulomatosis Rosacea Granuloma annulare	• Colonoscopy, inflammatory bowel disease panel
Toxic	Actinic granuloma Berylliosis Zirconium Hot tub lung	• Chest x-ray • Pulmonary function tests
Drug	Bacillus Calmette-Guérin NSAIDs Antibiotics Methotrexate	• Medication and immunization history from patient
Other	Lymphoid interstitial pneumonia	• Chest x-ray
	Hypersensitivity pneumonitis Chronic lymphocytic leukemia Lymphoma	• Complete blood count

alternative diagnoses were excluded and vaginal sarcoidosis emerged as the most likely diagnosis. Despite the fact that vaginal involvement is a rare manifestation of this multisystem disease, there are reports in the literature and this diagnosis is one of exclusion and is supported by the pathologic findings in this case. There are some serum markers that may be elevated in cases of sarcoidosis, including calcium, angiotensin converting enzyme, serum amyloid-A, soluble interleukin-2 receptor, lysozyme, and glycoprotein KL-6. In our patient we looked at serum calcium only. The fact that calcium was normal (9.2 mg/dL) and that other markers were not tested does not rule out sarcoidosis, as these are non-specific and are classically associated with pulmonary sarcoidosis (Miyoshi et al., 2010); our patient does not have evidence of systemic disease, specifically pulmonary involvement.

An additional interesting aspect of this case is the patient's history of endometrial cancer and associated treatment. Specifically, given this patient's history of a hysterectomy, we cannot rule this out as a chronic reactive response to prior surgery or suture material (Bardales et al., 1995). However, the patient is more than eight years out from surgery and the thickening did not appear at the vaginal cuff, so the likelihood of this as the cause for her physical exam findings and symptoms is thought to be unlikely. Additionally, no foreign body material was identified on physical exam or imaging.

This case report demonstrates that, although rare, sarcoidosis as well as other granulomatous processes should be considered when evaluating a patient with thickening of vaginal tissues or a vaginal mass, and prompt histological assessment is critical to diagnosis and treatment. There are reports of treatment with oral steroids, topical steroids, and methotrexate (Sahin et al., 2016). In our patient, oral steroids were required initially but ultimately she could be managed on topical corticosteroids and estrogen. It is also important to consult subspecialists to ensure thorough evaluation for other possible etiologies as well as obtain expert advice on appropriate treatment regimens and follow up.

Conflicts of interest

The authors report no conflicts of interest.

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