case report

Myometrial myxoidosis in a patient with systemic lupus erythematosus

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Myometrium myxoidosis is new terminology to describe a non-neoplastic process of extracellular mucinous accumulation in the myometrium wall of the uterus. We report a rare association of myometrial myxoidosis with lupus erythematosus in a 35-year old woman with a history of leiomyoma. At presentation, this case was diagnosed as a pelvic abscess and treated with specific antibiotherapy, and then discharged after clinical improvement. One week later, after recurrence of the symptoms, the patient underwent hysterectomy with bilateral salpingo-oophorectomy and appendectomy with anterior abdominal soft tissue part resection. Pathological analysis revealed diffuse hypocellular myxoid areas intersecting the smooth muscle layer of the uterus and cervix in addition to a focal area in the interstitium of smooth muscles of the appendix and soft tissue of the anterior abdominal wall. This case emphasizes the importance of distinguishing between myxoid neoplastic and non-neoplastic lesions with myxoid changes.

SIMILAR CASES PUBLISHED: To our knowledge, there are only two similar cases reported.

Uterine mesenchymal tumors comprise a set of diagnostically-challenging neoplasms that predominantly involve the smooth muscles of the uterus and endometrial stroma.[1] More specifically, myxoid lesions are uncommon and may be wrongfully-interpreted as myxoid leiomyomas.[2] Myometrial myxoidosis is a pseudo-neoplastic myxoid reaction of the myometrium and is believed to cause myometrial thickening due to abnormal accumulation of myxoid substances.[3] Differential diagnosis of such non-neoplastic lesions from other malignant uterine tumors seems plausible. In addition, its association with other systemic pathological conditions that may contribute to pathogenesis may be of considerable concern. In the present study, we report a rare association of myometrial myxoidosis with systemic lupus erythematosus (SLE) and review the relevant diagnostic features of this benign condition.

CASE

Presentation and history

A 35-year old patient presented to the emergency department with fever and abdominal pain evolving for about 3-4 weeks. The patient had a whitish vaginal discharge that started one month previously, followed by intermittent and dull abdominal pain and nausea without vomiting. A few days before presentation, she had severe suprapubic pain and fever with no dysuria, hematuria, bowel habits disorder or melena.

The patient had a history of SLE for the previous 4 years and had started prednisolone, methotrexate and hydroxychloroquine with a good therapeutic response. Surgically, she had a history of myomectomy, one year previously, for leiomyoma; the surgical report could not be reviewed because the intervention was done outside our hospital. The patient was never married and had no previous sexual activity before to exclude chronic inflammation secondary to sexually transmitted diseases, was nulliparous, having a regular menstrual cycle without menorrhagia, metrorrhagia or dysmenorrhea. There was no other medical history nor signs or symptoms of neurofibromatosis, scleroderma or other autoimmune disease.

Clinical examination and investigation

On examination, the patient was conscious and had a temperature of 38°C, a pulse of 95 beats/min, and 98/53 mm Hg blood pressure. On general examination, the skin was pale; no rash or pigmentation were noted. Abdominal examination revealed a soft lax abdomen, with a palpable suprapubic mass radiating to the right iliac fossa and this was associated with moderate tenderness over the area. The gynecological physical examination could not be done because the patient refused. Neurological clinical examination was normal. There was no evidence of palpable lymph nodes. The thyroid gland examination was normal. On radiological examination, a contrast enhanced CT-scan discovered two intra-abdominal collections; the first at the anterior extraperitoneal region measuring 6.6×4.1 cm and the second at the right iliac fossa measuring 3×3 cm. Other small subcutaneous collections were noted at the anterior midline abdomen. The uterus appeared bulky and hypodense; no well-defined lesion was identified. While both ovaries were unremarkable.

Management

The patient was admitted to the gynecology department for exploration of an abdominal collection. CT-guided drainage was performed at admission and a fluid culture showed positive non-typhoid *Salmonella*. Antibiotic therapy with ceftriaxone and metronidazole was started for the next ten days with rapid clinical improvement, including fever subsidence and a remarkable decrease in pain. The patient was discharged with metronidazole and cefuroxime for two weeks with a follow up appointment 2 weeks later. One week later, the patient presented again with fever and generalized abdominal pain. Surgery was indicated because of intractable chronic pelvic inflammatory disease and the patient underwent hysterectomy with bilateral salpingo-oophorectomy and appendectomy along with excision of a part of the anterior abdominal soft tissue. Intraoperative assessment showed firm adhesion between the bowel and posterior uterus wall with a myxomatous appearance of the uterus, along with a suspicious myxomatous anterior abdominal wall, which was also excised.

Macroscopy

All excised structures including the uterus, tubes and ovaries, as well as the appendix and a segment of anterior abdominal wall were macroscopically examined. The uterus showed a bulky enlargement measuring 13×10.5×7cm; and on section, the myometrial wall was diffusely thick (maximum thicknesses of 5cm), soft, tan and fleshy and dotted with small microcystic spaces filled with a clear fluid (**Figure 1**). Both ovaries and tubes were grossly unremarkable. The appendix measured 4.5×1.5 cm, the outer surface was congested and the mucosa was tan-pink. The segment of the anterior abdominal wall was soft and tan, measuring 5×3×2cm.

Microscopy

The entire section from the uterus showed hypocellular myxoid areas dissecting the smooth muscle bundles in a uterine section (**Figure 2a**). There was a multifocal mixture of chronic inflammatory cells and mucin-containing macrophages (muciphages) infiltrating the smooth muscle (**Figure 2b**). A chronic inflammation stigma was accentuated around the blood vessels [f] but no evidence of vasculitis was found (**Figure 2c**). The chronic inflammation and myxoid areas were also noted in focal areas of paratubal soft tissue of the fallopian tubes (**Figure 2d**), focal areas of muscle walls of the appendix (**Figure 2e**), cervix and soft tissue of the anterior abdominal wall (**Figure 2f, 2g**). The endometrium was weakly proliferative. The cervix mucosa, fallopian tubes and ovary were unremarkable. Alcian blue pH 2.5 and mucicarmine stains were diffusely positive in the interstitial myxoid of the myometrium (**Figures 3a & 3b**), whereas a Periodic acid–Schiff (without diastase) stain was negative (**Figure 4**). A gram-negative stain was negative. Immunohistochemistry showed that the myxoid hypocellular areas were positive for CD34 (**Figure 5**) and negative for S100, desmin, h-caldesmon smooth muscle action and anaplastic lymphoma kinase (ALK).

DISCUSSION

Myometrial myxoidosis is a newly recognized form of non-neoplastic myometrial change, which was first described by Veras et al in 2009.[3] It is viewed as extracellular accumulations of mucin in the myometrial wall.[3] We report a long-standing myxoid degeneration with chronic myometrial inflammation on a lupus

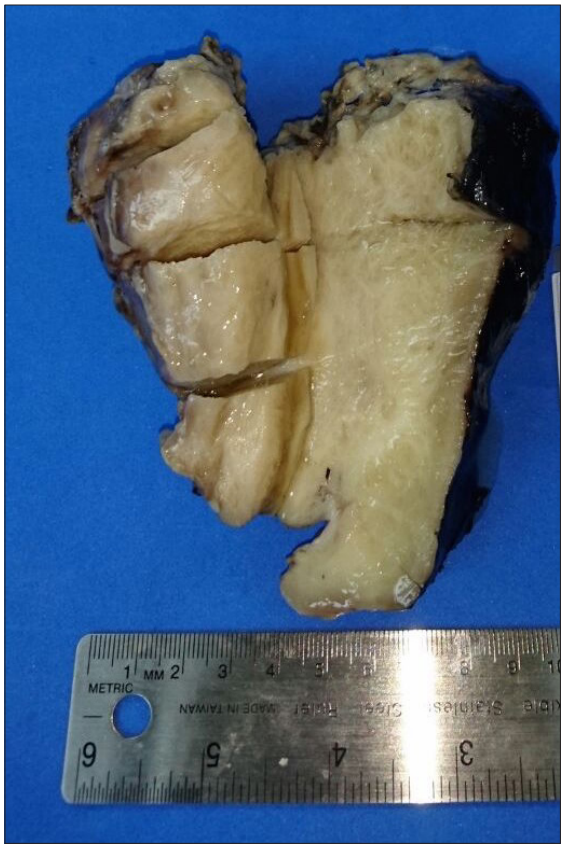

Figure 1. Gross image of the opened uterus, showing enlargement and thickened myometrium.

background. Myxoid changes in the uterus have been described in several neoplastic conditions, such as myxoid leiomyoma, myxoid stromal sarcoma and myxoid leiomyosarcoma.[4-6] Those lesions involving the myometrial wall in the absence of neoplastic growth are rarely encountered, with a total of seven cases reported;[2,3,7] of which two cases were associated with neurofibromatosis[2,7] and two other patients experienced SLE.[3] Our report adds another case of myometrial myxoidosis associated with SLE. **Table 1** summarizes all cases of myometrial myxoidosis.

SLE is an autoimmune disease characterized by vasculitis and chronic inflammation, which involves several organs including the skin, joints, kidneys, and gastrointestinal tract. The involvement of the gynecological system is rare; reported cases have presented with ovaritis, among other SLE manifestations.[8] However, the case under study presented with pelvic collection and bacterial infection, which is an unusual presentation. The main histological finding was a striking myometrial mucinosis as confirmed by a special stain involving the outer two-thirds of the uterus, the cervix, the upper half of the vagina, and the paratubal area of the fallopian tube tissue, abdominal wall and focal areas of the mesoappendix. This is different from the previously reported myometrial myxoidosis in that it was limited to the uterus and cervix.[3] We therefore suggest that the involvement of the uterus as well as the appendix and abdominal soft tissue may be a part of an unrecog-

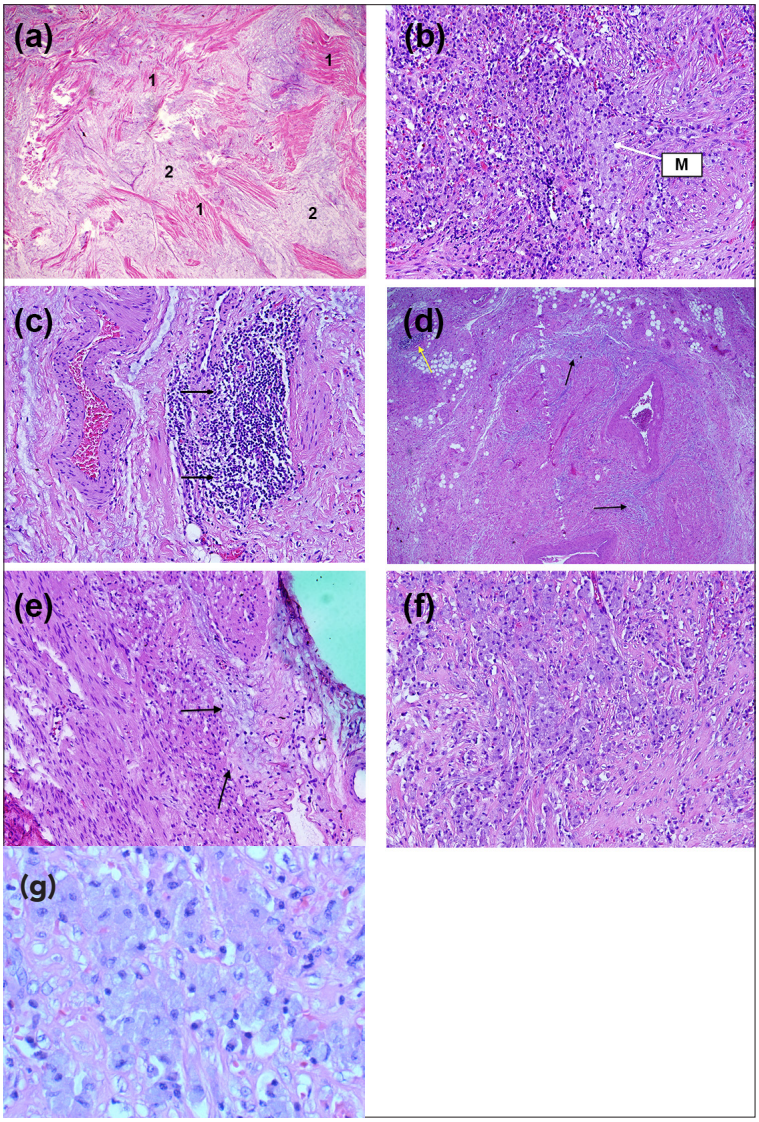

Figure 2. a) Uterus smooth muscle bundles interdissected by myxoid hypocellular areas; Hematolyn and eosin 4×. b) Mixture of chronic inflammation and mucinophages (arrow M) infiltrating the smooth muscle bundles; Hematolyn and eosin 10×; c) Lymphoid cells (arrows) aggregated around the blood vessels of uterus but no vasculitis; Hematolyn and eosin 4×; d) Paratubual soft tissue of fallopian tube showing myxoid areas (yellow arrow) and chronic inflammatory cells aggregates (black arrows); Hematolyn and eosin 4×; e) Appendix with focal myxoid areas (black arrows) in interstitium of between the smooth muscle bundles; Hematolyn and eosin 4×; f) Abdominal soft tissue shows chronic inflammation and mucinophages; Hematolyn and eosin 10×; g) High power mucinophages; Hematolyn and eosin 40×.

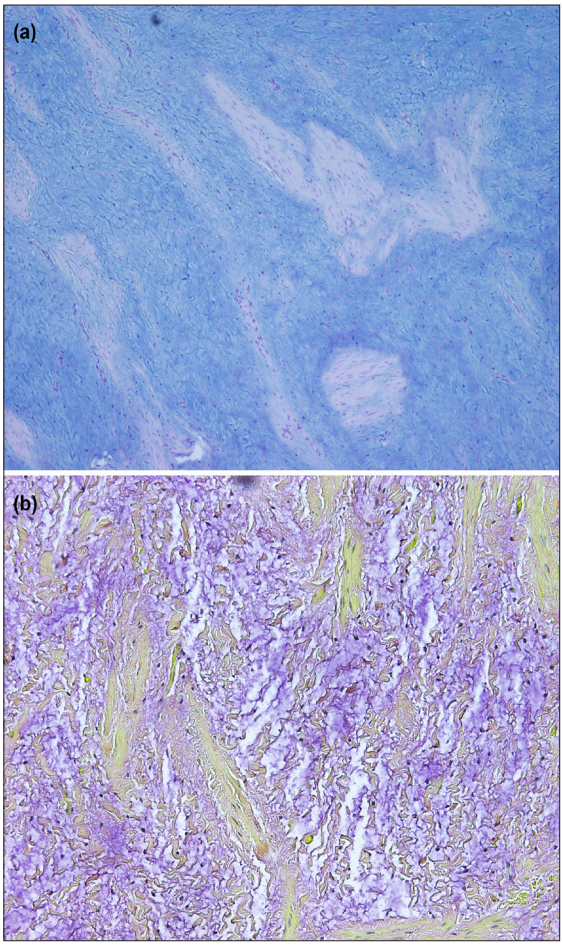

Figure 3. a) Alcin blue PH2.5, 4× and b) mucincarmin stain, are positive in uterus myxoid hypocellular areas, 10×.

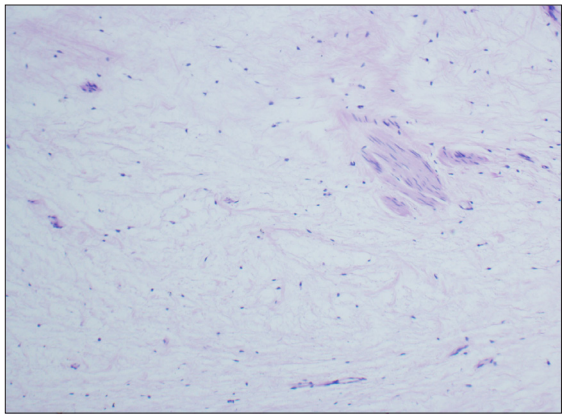

Figure 4. Periodic acid–Schiff (PAS) is negative, 4×.

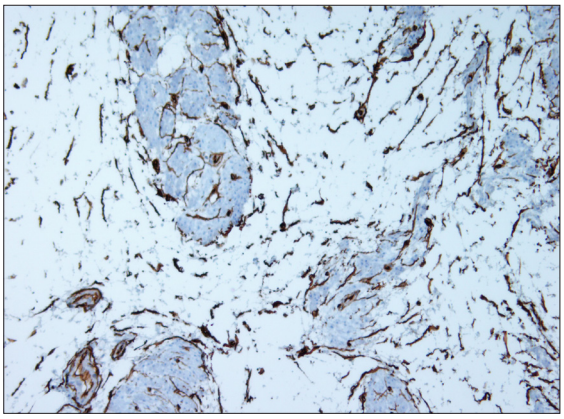

Figure 5. CD34 immunostain is positive in the myxoid hpocellular areas, 10×.

nized extension of SLE to the visceral organs.

The pathogenesis of myometrial mucinosis is uncertain. For our case, the association of lupus erythematosus raises the possibility of autoantibody- and cytokine-mediated stimulation of mucin production by myometrial fibroblast cells.[9] Other possibilities include inhibition of hyaluronidase activities that lead to suppression of mucin degradation, resulting in excessive mucin accumulation.[9] Interestingly, the interstitial myxoid lesions apparently mimic interstitial mucin deposition in patients with cutaneous lupus mucinosis.[10]

The abundance of myometrial and extrauterine myxoid involvement, including the peritoneum and appendix, highlights the importance of differentiation between myometrial myxoidosis and pseudomyxoma peritonei, which could be excluded due to the unremarkable epithelial surface lining of the appendix. Myometrial edema is another non-neoplastic condition that seems to be secondary to pregnancy[11] and hence could be excluded. In this condition, the stroma shows separation of the myometrium but, unlike mucinosis, the alcian blue pH 2.5 special stain is negative.

Other differential diagnoses among neoplastic conditions include myxoid leiomyoma, inflammatory myofibroblast tumor (IMT) and myxoid changes in endometrial stromal sarcoma. Generally, these neoplasms usually form a mass, which was not the case in our patient. Myxoid leiomyoma is a non-infiltrative tumor composed of trapped islands of smooth muscle in myxoid tissue along with a background of large vessels. These findings were not detected in our case. IMT is a soft tissue tumor composed of myofibroblasts with a mixture of plasma cells, lymphocytes and eosinophils. They were composed of elongated myofibroblasts containing abundant eosinophilic cytoplasm and vesicular nuclei. Myxoid changes can be found in the stroma of spindled myofibroblasts and fibroblasts, which was not seen in our case. IMT is positive to vi-

Table 1. Reported cases of myometrial myxoidosis.

Case; author	Clinical history	Morphology	Microscopic findings	Special stain	Immunohistochemistry
Veras et al[3] (case 1)	A 34-year case of SLE with symptomatic leiomyoma	Weight=673g; 5cm myometrial thickness; not well-defined lesion	Myxoid appearance, hypocellular; no myxoid changes in cervix, tubes or ovary	MC: weakly positive; PAS (without diastase): negative; AB,pH2.5:diffusely positive. Colloidal iron: diffusely positive	Not done
Veras et al[3] (case 2)	A 52-year case of SLE with ascites	Weight: 674g; myometrial thickness not reported; 3 nodules in myometrial wall	Myxoid appearance; hypocellular in between the non-myxoid leiomyoma; small lymphoid follicles noted; large arteries showing interstitial myxoid; cervix involved.	MC: weakly positive; PAS (without diastase): negative; PAS-AB, pH 2.5: diffusely positive for AB and negative for PAS; colloidal iron: diffusely positive; AB, pH 2.5: negative; AB, pH 1.0: weakly positive	Not done
McCluggage et al[2] (case 1)	A 48-year case of type 1 NF; menorrhagia + history of oral progestogens and Mirena coil, and total hysterectomy + bilateral salpingo-oophorectomy	Weight: 77gr with leiomyoma nodule	Multiple foci of hypocellular myxoid material; deep cervical stroma involved; myxoid foci in both the inner and outer halves of the myometrium	Not performed	Positive for CD34 and CD10. Negative for SMA, desmin, h-caldesmon, ER, S100 and ALK1
McCluggage et al[2] (case 2)	49-year-old; with subtotal hysterectomy and bilateral salpingo-oophorectomy	Weight: 250g; uterus totally necrotic and fibroid	Multiple foci of replacement of the myometrial smooth muscle outside the confines of the leiomyomas by hypocellular myxoid material; deep cervical stroma involved; myxoid foci in both the inner and outer halves of the myometrium	Not performed	Positive for CD34 and CD10. Negative for SMA, desmin, h-caldesmon, ER, S100 and ALK1
McCluggage et al[2] (case 3)	46 years; subtotal hysterectomy +bilateral salpingo-oophorectomy for complex hyperplasia endometrium; + history of Mirena coil use	500 g of uterus with leiomyoma	Nodule with single focus with myxoid focus; well circumscribed	Not performed	Positive for CD34 and CD10. Negative for SMA, desmin, h-caldesmon, ER, S100 and ALK1
McCluggage et al[2] (case 4)	38-year-old woman; presumed uterine fibroids	11 cm in maximum dimension; grossly myxoid myometrial	Smooth muscle extensively infiltrated by myxoid material	Not performed	Positive for CD34 and CD10. Negative for SMA, desmin, h-caldesmon, ER, S100 and ALK1
Pugh et al[7]	A 48-year case of type 1 NF asthma, hypertension, and postpartum pulmonary thromboembolism. Para 1, gravida 1	The uterus and cervix: 85×50×35 mm. Weight is not available	Infiltration of the isthmus and deep cervical stroma by well-demarcated nodules of paucicellular, myxoid material. No necrosis, or vascular invasion.	Not performed	Positive for CD34 and CD10. Negative for SMA, desmin, h-caldesmon, ER, EMA

ALK1: anaplastic lymphoma kinase; EMA: epithelial membrane antigen; ER: estrogen receptor; MC: mucicarmine; NF: neurofibromatosis; PAS: Periodic acid–Schiff; PAS-D: Periodic acid–Schiff–diastase; SMA: smooth muscle actin; SLE: systemic lupus erythematosus; AB:Alcian blue stain; MC: Mucicarmine stain.

Table 1 (cont.). Reported cases of myometrial myxoidosis.

Case; author	Clinical history	Morphology	Microscopic findings	Special stain	Immunohistochemistry
The present case	A 35-year-old patient; known case of SLE for 4 years; recurrent pelvic collection; underwent hysterectomy + bilateral salpingo-oophorectomy	Bulky enlarged uterus with thickened myometrium (5cm maximum thickness)	Diffuse hypocellular myxoid lesion dissecting the smooth muscle layer of uterus, cervix and pelvic organ	MC: diffusely positive AB, pH 2.5: positive; PAS and PAS-D: negative	Positive for CD34. Negative for CD10, SMA, desmin, h-caldesmon, ER, S100 and ALK1

ALK1: anaplastic lymphoma kinase; EMA: epithelial membrane antigen; ER: estrogen receptor; MC: mucicarmine; NF: neurofibromatosis; PAS: Periodic acid–Schiff; PAS-D: Periodic acid–Schiff–diastase; SMA: smooth muscle actin; SLE: systemic lupus erythematosus; AB:Alcian blue stain; MC: Mucicarmine stain.

mentin, alpha smooth muscle actin, muscle specific actin and calponin, along with ALK expression in 40% of cases; all were negative in our case. Endometrial stromal sarcoma is formed of monotonous ovoid to a spindly cellular proliferation with minimal cytoplasm proliferating around small arterioles. This neoplasm is positively reactive to beta-catenin in 67%, ER, PR, and CD10, all of which were negative in our case.[12] Immunologic IgG4-related disease is less likely in the differential diagnosis. It is composed of dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis and requires more than 40% of IgG4/IgG plasma cell ratio along with IgG4+ plasma cells more than 30 per high power field (HPF), which was not seen in our case. However, myxoid changes can occur in IgG4-related disease as a stromal reaction. However, the clinical, serological and radiological studies did not confirm a diagnosis of IgG4-related disease.

In conclusion, we report a very rare case of non-neoplastic myometrium myxoidosis associated with SLE, providing support to a hypothesized causal or pathogenic relationship between SLE and myxoid visceral changes. The crucial point, in this case, is for pathologists to be aware of the importance of the clinical history of the patient to correlate with histological changes and prevent over-interpretation of the findings as neoplastic lesions.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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