Endometriosis (EM) is a common gynecological disease that affects the endometrial glands and stroma outside the uterine cavity, mainly in the peritoneum, ovaries, and rectovaginal septum. It affects nearly 5%–10% of women in their reproductive years (ages 15–49 years), and its annual incidence is 0.1%. EM commonly presents with pelvic pain but can produce sciatic, obturator, or femoral nerve symptoms. Although the first histologically proven case was described in 1955 by Denton and Sherrill and more than a hundred of such cases have since been reported, the mechanism of nerve involvement with EM remains enigmatic. We present 2 cases of EM with sciatic neuropathy. We hypothesize that involvement of the lumbosacral plexus (LSP) in selected cases can be explained by perineural spread of EM from the uterus to the sacral plexus along the pelvic autonomic nerves and then further distally to the sciatic nerve or proximally to the spinal nerves. This explanation is supported by MRI evidence in both cases. As a proof of concept, the authors retrieved and analyzed the original MRI studies of a case reported in the literature and found a similar pattern of spread. They believe that the imaging evidence of their institutional cases together with the outside case is a very compelling indication for perineural spread as a mechanism of EM of the nerve.

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KEY WORDS endometriosis; sciatic nerve; sciatica; magnetic resonance imaging; autonomic pathways

Part I: Institutional Case Reports

Case 1

Presentation

A 49-year-old woman was referred to our institution in June 2013 with a diagnosis of lumbosacral plexopathy of unknown etiology. Her relevant medical history was significant for a ureteral stricture and cervical and lumbar spine degenerative disease. She had no history of EM.

History

Her symptoms started in October 2011 after she lifted a heavy object. She developed low-back pain radiating to the left buttock. Over subsequent months she gradually developed left lower-extremity weakness and numbness.

MRI of the lumbar spine done in May 2012 failed to reveal any significant abnormalities. MRI of the pelvis (Fig. I) performed in October 2012 demonstrated an amorphous
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Enhancing soft-tissue mass, thought to represent scar tissue or other granulation tissue, at the sciatic notch associated with the L-5 and S-1 spinal nerves. The mass extended along the L4–S1 spinal nerves proximally. The nerve themselves were hyperintense on T2-weighted images and enhancing on postcontrast scans. The gluteal musculature showed signs of acute and chronic denervation. PET/CT studies from October 2012 demonstrated an area of increased uptake at the sciatic notch compared with the surrounding normal musculature (Fig. 1B).

Examination

On neurological examination the patient had a left foot drop with markedly reduced strength in the left anterior tibialis (Grade 1/5), toe extensor (Grade 1/5), and peronei muscles (Grade 0/5). Her sensory examination showed reduction to pin and light touch over the left lateral calf and medial foot, with a qualitative sensation alteration to pin in the lateral foot and posterior thigh.

Electromyography conducted in June 2013 revealed a left lumbosacral plexopathy affecting the L-5 and S-1 myotomes associated with active denervation.

MRI of the LSP performed at the same time (Fig. 2), with and without intravenous contrast material, showed an ill-defined and slightly spiculated soft-tissue mass associated with the sciatic nerve at the sciatic notch. The mass itself was heterogeneous on T1- and T2-weighted sequences with cystic areas. Post-Gd scans demonstrated linear abnormality extending from the body of the uterus to the LSP or sciatic nerve proximal to the sciatic notch. The nerve itself appeared to be enlarged and infiltrated by the mass. A lesion with similar characteristics was discovered in the left obturator internus muscle. The gluteal musculature and obturator internus muscle exhibited signs of chronic denervation.

Procedure

A fine-needle aspiration biopsy of the lesion (Fig. 2F) was performed and revealed epithelial tissue with scant stroma positive for estrogen receptors (glands and stroma) and CD10 (stroma) (Fig. 3). The diagnosis of EM was established.

Postoperative Course

The patient was started on hormonal therapy. On follow-up 6 months later the patient reported resolution in pelvic pain and improved cyclic gluteal pain.

Case 2

Presentation

A 32-year-old woman with no relevant medical history presented to our institution in November 2000 with cata menial low-back, hip, and right lower-extremity pain accompanied by tingling in the distal leg.

History

Initially, in the fall of 1998 the patient noticed mild hip and pelvic pain, and numbness and tingling in the right lower extremity associated with her menstrual cycles. These symptoms progressively worsened.

MRI of the pelvis from February 2000 showed increased T2 signal along the right lateral pelvic wall involving the obturator internus and piriformis muscles. Changes were noted to be consistent with an inflammatory process and EM was suspected; however, a discernible endometrioma was not identified.

In March 2000 the patient underwent laparoscopy, which revealed peritoneal EM. She was started on gonadotropin-releasing hormone agonist treatment and experienced complete resolution of the pain. This therapy was discontinued after 4 months due to side effects, and the symptoms returned.

Examination

Electromyography done in November 2000 confirmed right sciatic neuropathy proximal to the innervation of the medial hamstrings. The abnormalities in the lumbar paraspinal muscles suggested involvement of the LSP.

MRI of the pelvis performed in November 2000 (Fig. 4) demonstrated a massively enlarged right sciatic nerve at the sciatic notch, which was hyperintense on T1- and T2-weighted sequences and heterogeneously enhancing on post-Gd scans. A similar heterogeneous abnormality with hemosiderin depositions was noted to be in the right piriformis and obturator internus muscles and in the right
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Based on the signal characteristics, these lesions were concluded to be foci of EM.

Treatment

EM was confirmed as the etiology based on the positive response to the gonadotropin-releasing hormone agonist, which the patient was started on in 2001. On follow-up 5 years later, the patient reported mild residual pelvic pain, no radiating pain, and improved ability to walk longer distances. MRI performed in 2005 demonstrated near-complete resolution of EM (Fig. 4D).

Part II: Retrospective Reinterpretation of a Previously Published Case

We wondered if our theory would apply to other cases in the literature. As a proof of concept, we retrieved a case reported by colleagues (Domínguez-Páez et al.) of a patient with right sciatic nerve EM. We reviewed the most recent MR images (2014) and MR images obtained 3 years earlier (2011). On the MRI from 2011 the sciatic nerve was massively enlarged and surrounded by heterogeneous tissue with focal hemorrhages suggestive of EM. As in our case we could follow the abnormality extending from the cervix to the right LSP, which also had similar imaging characteristics (Fig. 5A and B). On the 2014 MRI the sciatic nerve decreased in size, although it was still enlarged compared with its normal size as well as the L4–S1 spinal nerves. The spinal nerves (Fig. 5C and D) appeared identical to those in our Case 1 (Fig. 1C and D). We believe this case indeed represents another example of perineural spread of EM and further strengthens our theory.

Discussion

We propose that perineural spread from the organ to the LSP, demonstrated in pelvic cancer including cervical cancer, applies to EM as well and represents an alternate mechanism in selected cases. The possibility of EM tracking along the nerves as a form of spread was described by Possover et al.; however, such an anatomical, mechanistic explanation as the one described in the present report has not yet been postulated. We provide compelling evidence by presenting our 2 cases and the previously published case that showed signs of perineural spread.

We hypothesize that endometrial glands and stroma infiltrate the uterine plexus, part of the inferior hypogastric plexus (IHP). From the IHP, EM continues to grow toward the sacral plexus along the sacral and pelvic splanchnic nerves and toward the lumbar plexus along the hypogastric nerves (Fig. 6). Within the plexus, EM can spread proximally to the spinal nerves (Figs. 1C and D and 5C and D) or distally to the arborizing nerves. We were surprised by the presence of EM in the pelvic muscles (Figs. 2D and E and 4A and B) and pelvic bone (Fig. 4A and B) in a pattern similar to that which has been described for perineu-
ral spread of malignant cancer to muscle and bone. We theorize that these deposits could result from perineural spread of EM along the motor and bone branches from the LSP. How EM invades the uterine plexus is not clear. Up to 90% of women with EM have adenomyosis, and deep adenomyotic nodules have been demonstrated to be closely associated with nerves. We theorize that endometriotic cells and stroma can propagate from deep adenomyotic nodules along the fine uterine nerves toward the IHP in the uterosacral ligament (Fig. 2D and E) and then as described above. The perineural spread as a possible explanation is supported by reciprocal interactions between EM and nerves. Not only does EM promote neurogenesis, but in turn the nerves promote angiogenesis and EM growth. EM can be classified into several subtypes, of which deep infiltrating endometriosis (DIE) seems to be the most aggressive and most challenging to treat due to its invasive nature. DIE is more painful than other forms of EM, which can be explained by its propensity to invade and extend along the pelvic nerves. DIE can cause ureteral or rectosigmoid strictures and sacral plexus entrapment requiring demanding reconstructive surgeries. Intraneural invasion of major somatic nerves such as the sciatic or obturator nerve prevents complete resection. DIE can also be more challenging to diagnose as it may have no peritoneal manifestation at all or may present only with peritoneal “pockets,” probably caused by subperitoneal scarring and retraction.

Possover et al. were the first to propose a “neural hypothesis,” describing a major role of the pelvic nervous system in EM. To support the theory, they correlated common locations of DIE with major components of the pelvic sympathetic system. Although the parasympathetic system might be implicated as well, other authors have observed a similar distribution of DIE.

EM is heterogeneously hyperintense on T1-weighted MRI due to blood collections and hypointense from hemosiderin depositions. On T2-weighted MRI, it has a similar heterogeneous appearance. Typical, but very nonspecific, is retraction of surrounding tissue due to scarring. The perineural spread can be visualized as an abnormality extending from the uterus toward the LSP (Figs. 2A and 5A and B), which is hyperintense on T2-weighted MRI and avidly enhancing on post-Gd scans. The LSP and branching nerves infiltrated with EM are enlarged, hyperintense.
Perineural spread of endometriosis on T2-weighted MR images, and heterogeneously enhancing on contrast-enhanced images.

We understand that intraperitoneal seeding with subsequent nerve compression is the most probable explanation for most cases with neural symptoms. A review of the literature revealed several other cases of interest. These can be divided into 2 subgroups: 1) cases with nerve involvement and no peritoneal disease; and 2) cases with intraneural (e.g., intrasciatic) EM with either unspecified or some peritoneal disease. Pham et al.\(^{35}\) reported a case in a patient presenting with sciatic nerve weakness. At the time of presentation, the patient had no peritoneal disease, and on biopsy EM was found in the epineurium. Interestingly, gluteal and pelvic muscles demonstrated denervation, pointing to a more widespread process. Torkelson et al.\(^{46}\) reported 2 cases, one of which had no peritoneal disease and intraneural EM of the sciatic nerve. Ceccaroni et al.\(^{13}\) reported another case of sciatic nerve EM and no peritoneal disease. Several authors, however, reported cases of intraneural sciatic nerve EM, which could be explained by perineural spread.\(^{24,30,31,43,56}\)

We wonder if cases of EM with nerve and bone or muscle involvement could be explained by perineural spread along the periosteal and muscle branches. Redwine and Sharpe\(^{40}\) reported a case of obturator nerve EM extending to the ilium. A case of sciatic nerve EM that spread to the femur was described by Oei et al.\(^{33}\) Also, the second case of sciatic nerve EM reported by Torkelson et al.\(^{46}\) had EM in the ischial tuberosity in a pattern that was reminiscent of that described in perineural spread of cancer.\(^{8}\) We further hypothesize that cases of conus medullaris EM could be explained as an extension of the same process intradurally along the sacral and lumbar nerve roots,\(^{20,44}\) possibly with subsequent intradural seeding\(^{19}\) as proposed in perineural spread of prostate cancer.\(^{16}\)

Limitations

We understand that our article has several limitations. It is based on 2 individual cases, and further research is needed to confirm perineural spread of EM as an alternative explanation for sciatic nerve EM. We acknowledge that the theory of retrograde menstruation with intraperitoneal seeding first proposed by Sampson\(^{7,41}\) is the likely explanation for most cases of sacral plexus EM. We pro-

FIG. 4. Case 2. MRI. An axial T2-weighted MR image (A) demonstrates heterogeneously increased signal in the enlarged right sciatic nerve (ellipse). The obturator internus muscle is infiltrated with a heterogeneous hyperintense soft-tissue mass with hemosiderin depositions (thin arrow). The muscle itself and the piriformis muscle (arrowheads) show diffusely increased signal suggestive of denervation. Another nodulus of similar characteristics is observed in the right ischium (thick arrow). The same structures demonstrate prominent heterogeneous enhancement on axial T1-weighted Gd-enhanced MR imaging (B) (thin arrow: obturator internus muscle; thick arrow: ischium; arrowheads: piriformis muscle; ellipse: sciatic nerve). An axial T2-weighted image (C) demonstrates a massively enlarged and infiltrated right sciatic nerve at the sciatic notch (arrowhead). An axial follow-up T1-weighted image (D) obtained 6 years later shows marked improvement of the sciatic nerve enlargement (arrowhead).

FIG. 5. Outside case. MRI. An axial T1-weighted Gd-enhanced image (A) demonstrates an enhancing abnormality extending from the cervix (asterisk) to the sciatic notch and the sciatic nerve (dashed arrow). A coronal T2-weighted fat-saturated image (B) demonstrates the same hyperintense and heterogeneous abnormality (dashed arrow) extending from the cervix (asterisk). Coronal fat-saturated fast spin echo images (C and D) from an MRI examination performed 3 years later show the hyperintense and enlarged right S-1 and L-4 spinal nerves demonstrating signs of perineural spread (C, dashed arrow, the S-1 spinal nerve; D, dashed arrow, the L-4 spinal nerve).
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Vide a secondary explanation applicable to selected cases supported by compelling evidence based on imaging studies and review of the literature. Vercellini et al. reviewed the reported cases of sciatic nerve EM published until 2002 and found that the right sciatic nerve was significantly more involved than the left sciatic nerve. They proposed that this could be explained anatomically as the sigmoid “protects” the left sacral plexus. However, when we used the same methodology, reviewed all cases they referenced, and added all cases published until the time of writing (47 new cases), we could not confirm their finding—there was no statistically significant difference between the left and right side. We acknowledge other possible explanations such as lymphatic or hematogenous spread, but none of these theories would explain a continuous band of EM extending from the uterus to the sacral plexus as seen in the imaging evidence presented here. Separated, individual lesions (e.g., EM focus in lungs) would be expected with hematogenous or lymphogenous spread. None of our patients had evidence suggestive of such lesions; in addition, this has been excluded in our Case 1 by whole-body PET/CT scanning.

Conclusions

We described the cases of 2 patients with sciatic nerve EM. We demonstrated that our theory is applicable to other cases reported in the literature. We theorize that both can be explained by perineural spread of EM from the uterus to the sacral plexus along the visceral autonomic nerves. From the plexus, EM can spread proximally to the spinal nerves or distally to the sciatic nerve or pelvic bone and musculature using bone and muscle nerve branches. Such a complete, mechanistic explanation for selected cases of EM presenting with nerve symptoms has not, to our knowledge, been presented until now.

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