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Case Report

Acute Appendicitis and Periappendicitis Revealing Squamous and Transitional Cystic and Solid Nests in Adult Patients: Metaplasia or Vestigeal Remnants?

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Squamous metaplasia of the appendix serosa is rare. We aimed to report the clinical and morphological features of 3 such cases. The patients presented with abdominal pain (n = 1 man, 2 women; age range, 29–35 years). The clinical diagnosis was appendicitis/ periappendicitis (in the context of hydro/pyosalpinx). The surgical resected appendix showed several cystic and solid epithelial nests (1 mm and less) in the serosa/subserosa. Epithelial cells expressed p63, cytokeratin 5/6, as well as cytokeratins 7, 20, and CD10. Cystic and solid squamous and transitional epithelial nests of the appendix subserosa/ serosa in adult patients may be revealed by acute appendicitis/ periappendicitis. The presence of such lesions, metaplastic or vestigial in nature, should be acknowledged since they can be misdiagnosed with metastatic epithelial tumor nests or they may undergo malignant change.

Key words: Epithelial – Metaplasia – Squamous – Transitional – Remnant – Adult – Acute Appendicitis – Periappendicitis – Appendix – Immunohistochemistry

Squamous metaplasia of the appendix serosa is rare, to our knowledge reported in 6 patients in 1950 and 1997.[1–3] More recently, in the 4 large reported series of appendectomies, one case of squamous metaplasia is mentioned.[4–7] Few data are available on the clinical contexts.

Here we report 3 rare cases in which cystic and solid foci of squamous and transitional epithelial tissue were revealed by acute appendicitis. These lesions were diagnosed in the subserosal and serosal appendix, at microscopic examination of the appendectomy specimen.

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Case Reports

The first patient (man, 53 years) presented with acute abdominal pain for 5 days, recent dysuria, and hyperleukocytosis with neurophilia. The patient's history showed right hip prosthesis and several knee meniscus resections. The computed tomography scan (CT scan) showed appendicitis in the internal and laterocecal region with a parietal defect proximally and, extradigestive air cavities (Fig. 1). Right colon diverticuli were present, and the liver, pancreas, spleen, kidneys, bladder and ureters (at distance of the appendix region), and bones were normal. On preoperative coelioscopic examination, the appendiceal zone was inflammatory. Microscopic examination of the appendectomy specimen showed acute panappendicitis (predominantly of the base of the appendix) with inflammatory peritoneal reaction. In this region, at proximity to the appendix muscle wall and along the inflamed serosa/subserosa over a length of 4 mm, there were 6 round or oval epithelial nests (less than 1 mm; Fig. 1). The subserosa showed diffuse edema and inflammation. The nests did not protrude in the peritoneal cavity; rather, they were in the reactive subserosa covered by the fibroinflammatory periappendicits. Three cystic nests (without papillae) were seen on other appendix fragments (other tissue blocks; Fig. 1). These epithelial nests were surrounded by a focal thin fibrous, collagen layer. The stratified epithelium showed a wide spectrum of aspects from completely solid nests to cysts lined by a flat, completely atrophic epithelium. In the solid or partly cystic nests, the epithelial cells were large, with visible cell borders. Focally, luminal and basal cells, spindle-shaped, showed less cytoplasm. Mild atypia, without mitoses, were present, and the nuclear/cytoplasmic ratio was low. On immunohistochemistry, the epithelial cells (nests, cystic or not) expressed cytoplasmic cytokeratin CK5/6, nuclear p63 and did not express calretinin or WT1 (Fig. 1). Diffuse CK7 and, focal and luminal, membrane or cytoplasmic CK20 expression were observed in the cyst cells. Perimembrane CD10 was expressed in rare cells of the solid nests. Very few nuclei expressed Ki67. There was no CD31-positive endothelial cells around the epithelial nests. Postoperatively, the patient showed fever. A 4-cm liquid collection in the Douglas and Morison spaces (*E. coli penicilinase* positive) was seen on computed tomography scan, and was treated with drainage, metronidazole, and ceftriaxone. The patient was released 7 days postoperatively with no complaints.

The second patient (woman, 29 years) presented with constipation (despite sodium citrate/sodium lauryl sulfoacetate/sorbitol 70% treatment), nausea, asthenia, right abdominal pain, and showed hyperleukocytosis (17,000). The patient's history revealed hypothyroidia (diagnosed at the age of 8 years); Crohn and celiac disease (diagnosed at the age of 28 years); Gougerot-Sjogren syndrome and, uterine retention post-medical abortion (diagnosed 3 weeks before). The patient had hydroxychloroquine, corticoid, levothyroxine, and estroprogestative treatment. The CT scan revealed diffuse colon stercoral stasis and pelvic cecum. A second CT scan showed peritoneal collection in the Douglas space, a right laterouterine mass measuring 5×3 cm with a 1.5-cm cyst suspect of hydro/pyosalpinx, and an appendix slightly increased in size. The clinical diagnosis was that of hydrosalpinx/pyosalpinx. Coelioscopic appendectomy was performed and right salpingotomy. The appendix measured 7.5 cm. The microscopic examination revealed foci of acute mucosal inflammation with epithelial erosions (and melanosis) associated to acute diffuse inflammation of the muscle and subserosal/serosal layers. Two subserosal cysts were identified on tissue specimen from the mid-appendix (Fig. 2). One of the cysts was 1 mm in size and dislocated the appendiceal muscle layer. The 2nd (solid on serial sections, smaller in size) was situated in the mesoappendix subserosa at 3.5 mm from the circular appendiceal muscle layer. The latter cyst was surrounded in part by smooth-muscle cells (Fig. 2). In both structures, the epithelium was pluristratified, with inflammatory exocytosis. No keratin was seen. Both lesions were not identified on the serial sections stained for cytokeratin 5/6 and p63. A focal positive reaction in the unilayered reactive mesothelium was observed for CK5/6 while p63 was not expressed. At 3 weeks postoperatively, the patient was well.

The third patient (woman, 32 years) presented with abdominal pain, fever, and hyperleukocytosis (14,000). The patient's history revealed lumbar discopathy L5S1 (ibuprofen treatment), cholecystectomy (laparoscopic), and allergy to penicillin. The CT scan showed a latero- and retrocecal appendix, increased in size (16 mm diameter) at the base, and containing a 1-cm sized stercolith. The periappendiceal fat was infiltrated. A 13-mm subcapsular liver simple cyst was also identified. Laparoscopic appendectomy was performed. The appendix measured 12.5 cm and showed acute appendicits and peritonitis on microscopy. A subserosal cyst (1 mm

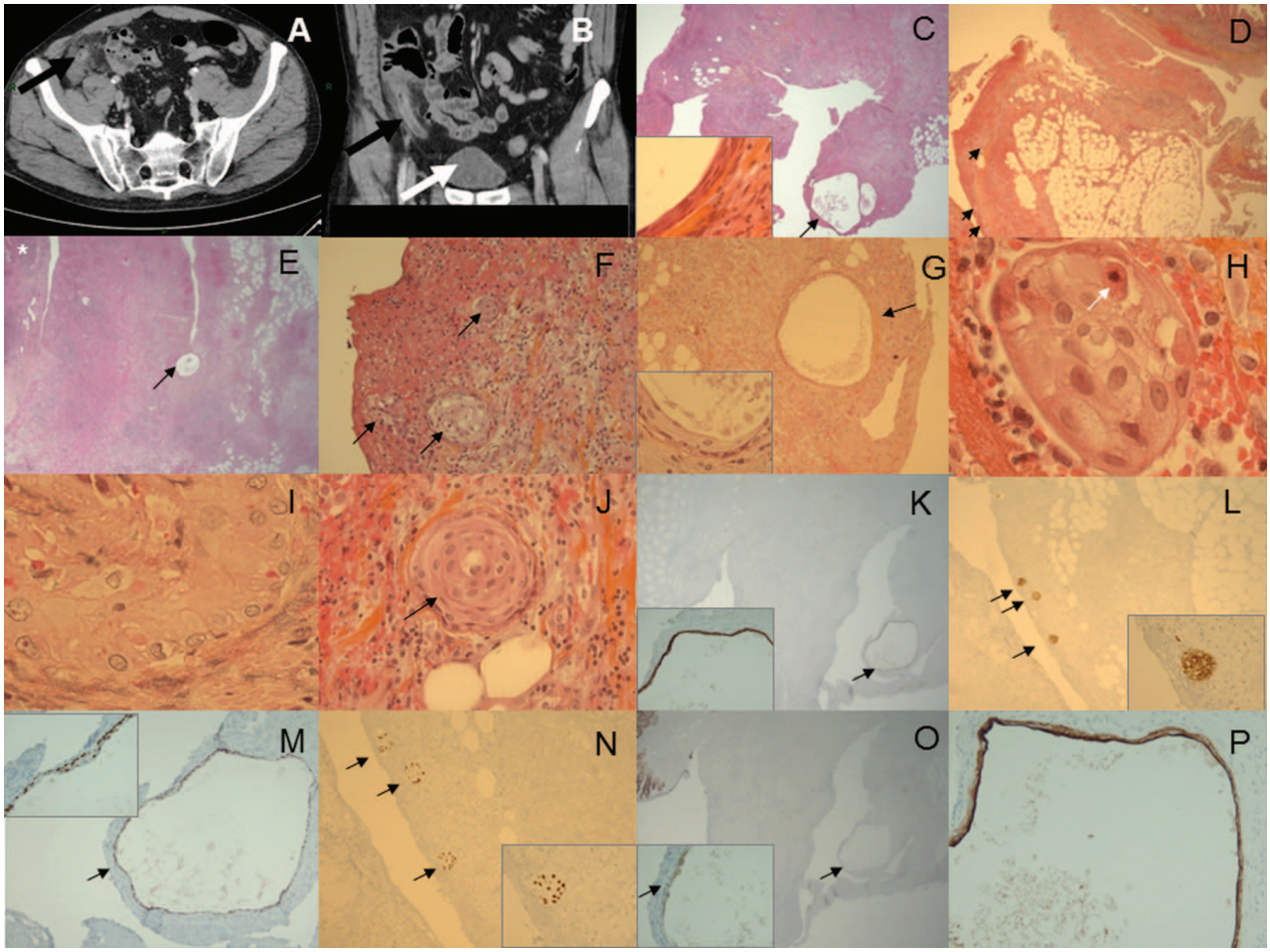

Fig. 1 For the 1st case, on CT scan the appendiceal region was inflammatory with pneumoperitoneus cavities ([A], black arrow). The CT scan reconstruction (B) showed the inflammatory appendix (black arrow) at distance from the urinary bladder (white arrow). On microscopy, the epithelial nests, cystic (C, C inset, E, G) or solid (D, F, H–J) were observed in the appendix subserosa. The epithelial stratified lining consisted in large cells with pale pink cytoplasm or showing varied degrees of atrophia (C–J). A focal collagen rim surrounded the nests (G, J). Rare apoptosis/dyskeratosis were seen in the epithelial nests (H). Black arrows indicate epithelial nests, white stars indicate appendix mucosa (C–E). The epithelial cells expressed cytokeratin 5/6 (K, K inset, L, L inset) and p63 (M, M inset, and N, N inset). They also expressed focally cytokeratin 20 (O, O inset) and diffusely cytokeratin 7 (P). The black arrows indicate the epithelial nests. Original magnification: ×2.5 (C–E, K, L, O); ×10 (G); ×20 (F, J); ×40 (C inset, G inset, H, I, K inset, L inset, M inset, N inset, O inset, P).

in size) was identified on the section made at the site of cecal resection, the appendiceal muscle layer being compressed by the cyst. The cyst was lined by a continuous atrophic, stratified epithelium (Fig. 2). The immunohistochemistries were noncontributive since the lesion was not identified on these serial sections. Postoperatively, the patient showed abdominal pain in the right iliac fossa. A CT scan guided punction was performed from the pelvic liquid (negative in culture). At 3 weeks post-appendectomy the patient was well, without fever or pain.

Discussion

Here we report 3 cases, in which microscopic cystic and solid nests of squamous and transitional epithelial epithelium, located in the subserosa of the appendix, were revealed by acute appendicitis. Similar findings in our opinion, have been reported by Crome[1] and by Michal[2] both in women and men. More recently, one case of squamous metaplasia is mentioned in the series of unusual appendiceal findings by Charfi *et al*.[6] Interestingly, solid nests, as seen in 2 of the cases we report, have been

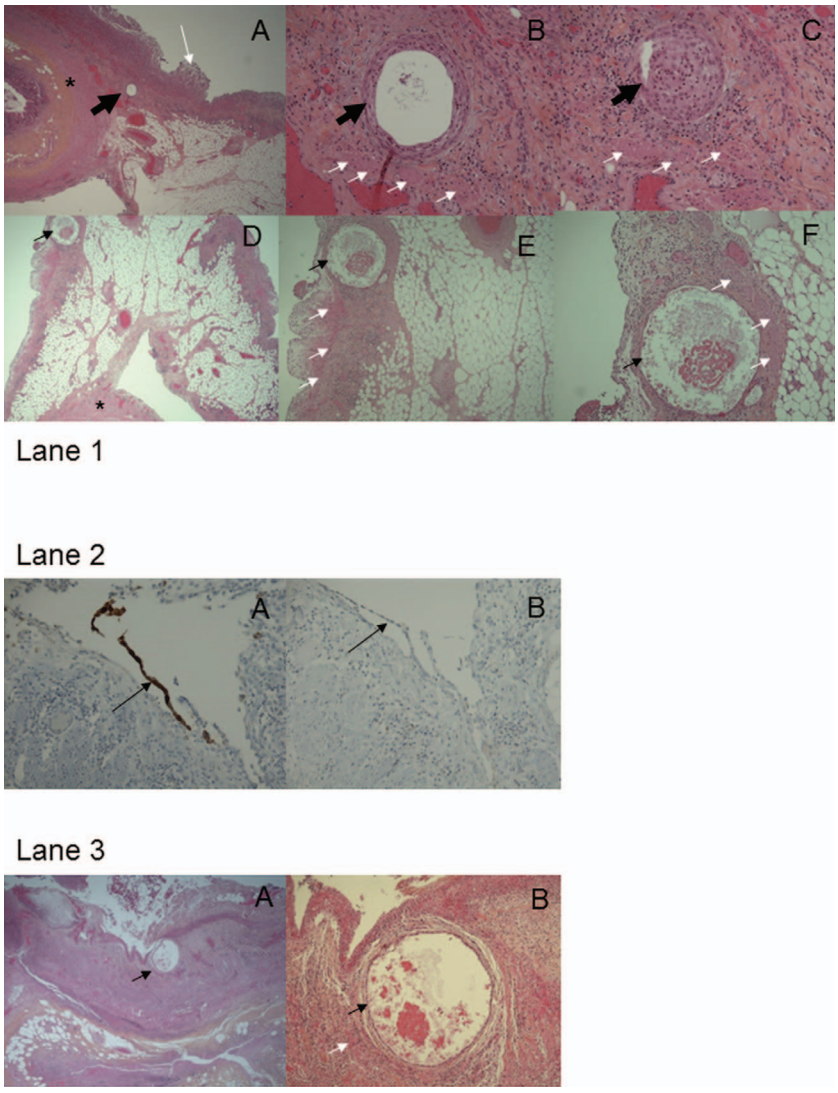

Fig. 2 Lane 1: In the 2nd case, the cystic and solid epithelial nests were located in the subserosa (B and C serial sections of the same lesion; A: white arrow/peritonitis). Smooth muscle cells (B, C, E, F: white arrows) surrounded in part these epithelial structures (A–F: black arrows). One of these structures was situated at distance (3.5 mm) from the circular appendiceal muscle layer. Inflammatory exocytosis was observed in these epithelial structures. Original magnification ×2.5 (A, D), ×5 (D), ×20 (B, C), ×40 (E); asterisk/appendiceal muscle layer. Lane 2: Reactive unilayered mesothelial cells expressed cytokeratin 5/6 (A, arrow) and did not express p63 (B, arrow). Original magnification ×20 (A, B). Lane 3: In the 3rd case (A, B), the cystic subserosal/serosal epithelial nest (black arrow) was surrounded by inflammatory cells and dislocated the appendiceal muscle layer (white arrow). Original magnification ×2.5 (A), ×10 (B).

mentioned in 3 out of the 7 published cases—to our knowledge. However, associated acute appendicits as in the present cases is reported in 1 of the patients only.[1] In the 2nd case we report appendiceal mucosal inflammation was mild possibly related to the known Crohn disease the patient had, although without associated classical architectural changes or granuloma. The diffuse serosal/subserosal and muscular inflammation seen in the same appendix were rather thought to be related to the salpingeal lesions and not a persistent digestive inflammation after the medical treatments the patient had. However the salpingeal lesions have not been microscopically examined.

Coelomic prosoplasia is thought to result in similar tissue types in rabbit experimental pleura models.[8] Extensive microscopic examination is required for the diagnosis of these minute, heterogeneous, multifocal lesions, solid and cystic. Interestingly, no typical keratin deposits were identified. Microscopic cytological features suggested rather immature or incomplete squamous metaplasia, however with some apoptotic or dyskeratotic cells. Presence of cytokeratin 20 and CD10 expression further indicated a possible transitional-type differentiation. A thin fibro-collagen layer was also observed around some of the round-shaped epithelial nests. These aspects, reminiscent of von Brunn's nests, along with the lack of reactivity for the mesothelium-markers calretinin and WT1, may suggest an origin from the allantoid urachus. Moreover, in 1 of the patients, the cyst was surrounded in part by a muscle layer, situated at distance from the appendiceal muscle layer. Inter-

estingly, reactive unilayered mesothelial cells expressed CK5/6 and not p63. The main differential diagnoses, those with malignant tumors, mesothelial, squamous, or urothelial, were ruled out as based on the presence of regular cystic change, as well as based on the presence of abundant cytoplasm, and of the lack of desmoplasia. Our observations on standard hematoxylin-and-eosin stained slides were comforted by the lack of CD31 positive endothelial cells around the nests, as suggestive of emboli, and, by the presence of very rare Ki67 positive nuclei. Radiological and preoperative examination allowed us to rule out the possibility of diverticula or developmental abnormalities, urothelial, ureteral, vesical, or colorectal, entrapped in the periappendiceal inflammation.

In conclusion, we report 3 rare cases of cystic and solid squamous and transitional epithelial nests located in the appendix subserosa. These lesions, diagnosed in adult patients, were revealed by acute appendicits and periappendicitis. Although extensive sampling and microscopic examination including immunohistochemical examination, the nature of the lesions—whether metaplastic or vestigial—cannot be precised. However, the presence of such lesions should be acknowledged since they can be misdiagnosed with metastatic epithelial tumor nests or they may undergo malignant change themselves.[3]

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