CASE REPORT

Squamous-Lined Cyst of Pancreas with unusual Plexiform Neuronal Hyperplasia: A Case Report and Review of the Literature

Aoife J McCarthy, Runjan Chetty

Department of Pathology, Laboratory Medicine Program, University Health Network and University of Toronto, Toronto, Canada

ABSTRACT

A 61-year old female presented with a unilocular cyst in the tail of the pancreas. The cyst was lined partly by squamous and low-cuboidal epithelium and did not communicate with the pancreatic ductal system. Much of the lining was denuded with underlying mixed inflammation and extensive fibrosis. No ovarian stroma was identified despite extensive sampling and immunohistochemical staining. An additional curious finding was that of extensive neuronal hyperplasia surrounding the cyst wall. It consisted of nerves bundles of varying size and had a distinct plexiform pattern. The patient did not have a history or the clinical stigmata of neurofibromatosis. This is an unusual case of a primary squamous or epidermoid cyst of the pancreas with associated reactive plexiform neuronal hyperplasia.

INTRODUCTION

Advances in imaging and interventional/surgical techniques and the sharp drop in the mortality rate of pancreatic surgery have rendered pancreatic biopsies and resections common-place specimens. Although cystic tumors of the pancreas are still relatively rare, they constitute an important category of pathologically heterogeneous pancreatic lesions, ranging from non-neoplastic to malignant neoplastic cysts, with a challenging differential diagnosis at the clinical, radiological, and pathological levels.

Cysts that are lined by squamous epithelium range from relatively benign post-obstructive lesions (e.g. squamoid cystosis) to neoplastic cysts where the squamous epithelium is an integral part of the lesion, as seen in the case herein.

Given the rarity of pancreatic cysts lined by squamous epithelium, these lesions can be challenging histologically. In this report, we explore the differential diagnosis of squamous-lined cysts of the pancreas and undertake a pertinent review of the literature.

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Correspondence Aoife McCarthy
Department of Pathology, Laboratory Medicine Program
University Health Network, Toronto General Hospital
200 Elizabeth Street, 11th Floor, Eaton Wing
Toronto General Hospital
Toronto, Ontario, M5G 2C4
Canada
Tel (416)-340-5319
Fax (416)-340-5517
E-mail aoife.mccarthy@uhn.ca

CASE REPORT

We report a case of a 61 year old female who had been having imaging surveillance of a 4.5 cm unilocular cyst in the pancreatic tail since 2013 when it was detected radiologically during a hospital admission for an episode of idiopathic pancreatitis. The most recent imaging showed that the cyst measured 5 cm and there was no evidence of a mass or lymphadenopathy. The patient underwent a distal pancreatectomy, which disclosed a 5.1 cm, uniloculated pancreatic cyst that did not communicate with the main pancreatic duct or rest of the ductal system. She had been asymptomatic, was otherwise well and was a non-smoker and non-drinker.

The entire cyst was examined histologically and was partially epithelial-lined, focally by non-keratinizing squamous epithelium and focally by low columnar/cuboidal epithelium **(Figures 1a, 1b and 1c)**. The majority of the cyst lining was denuded and was replaced by granulation tissue **(Figure 2)**. Extensive mixed acute and chronic inflammation, fibrosis and hemosiderin were present and ovarian-type stroma was not identified morphologically or by immunohistochemistry. There was no evidence of epithelial dysplasia or malignancy, and heterotopic or accessory splenic tissue was not identified. The background pancreas showed no evidence of chronic pancreatitis. The features were most compatible with a benign epidermoid (squamous) cyst of the pancreas.

In addition, striking neuronal hyperplasia was present in the pancreatic parenchyma adjacent to the cyst, as well as in the pancreatic parenchyma remote from the cyst. It was characterised by a prominent proliferation of bundles of spindle cells exhibiting S100-protein positivity in a plexiform pattern **(Figures 3a, 3b and 3c)**. Such florid neuronal hyperplasia has not previously been described

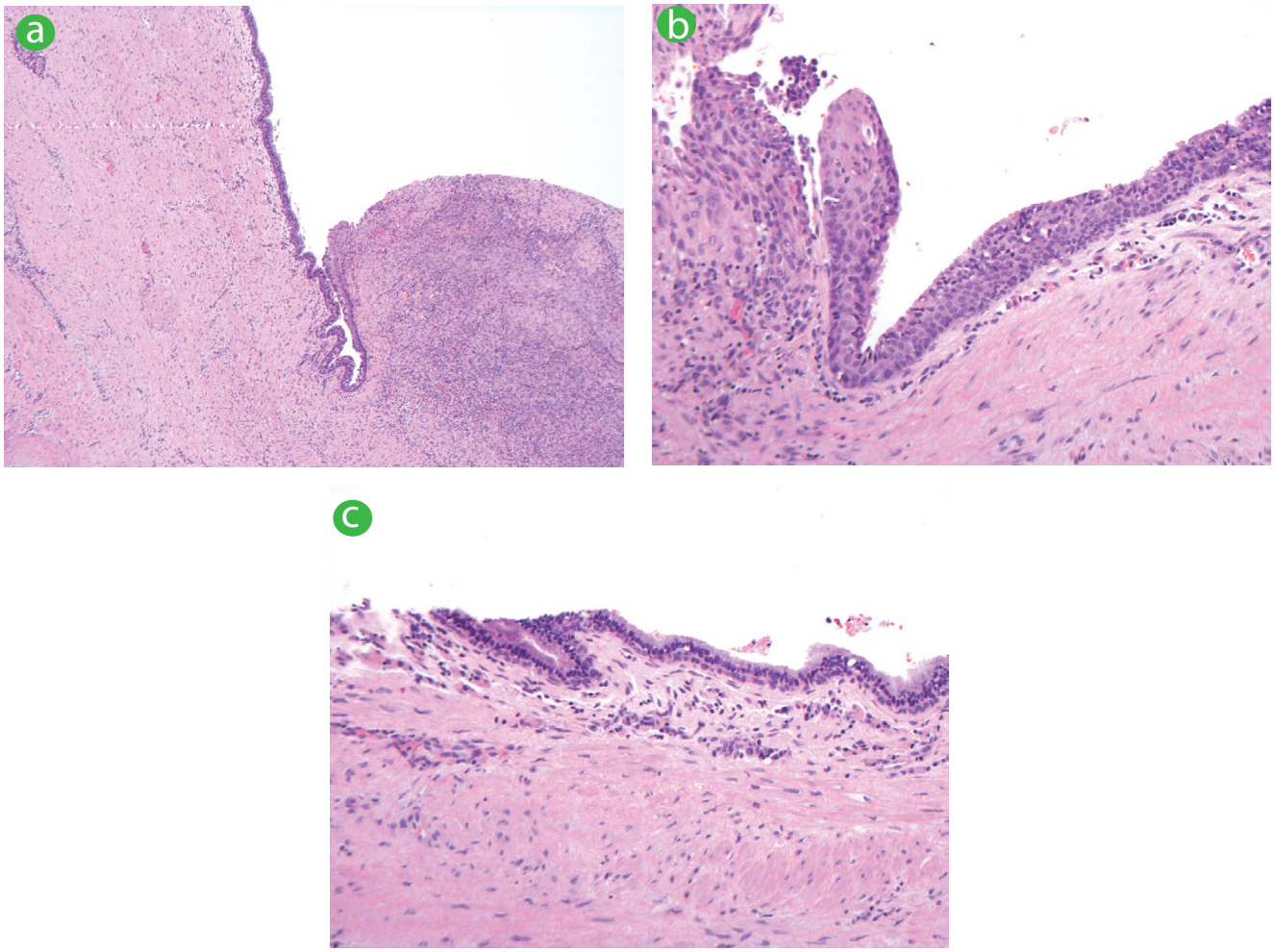

Figure 1. The pancreatic cyst was partially epithelial-lined (**1a**, x50), lined focally by non-keratinizing squamous epithelium (**1b**, x200) and focally by low columnar/cuboidal epithelium (**1c**, x200). All H&E.

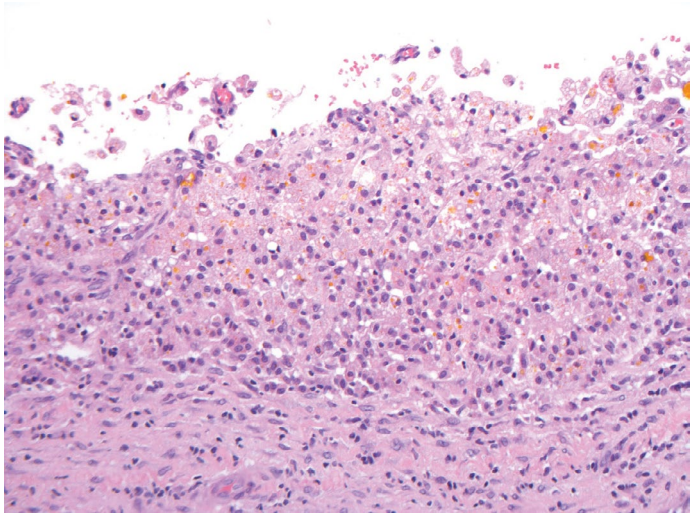

Figure 2. The majority of the cyst lining was denuded and was replaced by granulation tissue (H&E, x200).

in the pancreas. Furthermore, the patient did not have neurofibromatosis.

No further therapy was required for our patient. Four months post-surgery, she is well, and has had no complications.

DISCUSSION

Cystic tumors of the pancreas are significantly less common than solid ones, but up to 15% of resection specimens in some institutions have been reported to disclose cystic lesions [1]. Pancreatic resection specimens, and thus pancreatic cystic lesions, have become more prevalent in surgical pathology departments in recent years, due to a combination of developments in imaging techniques, with increased detection of clinically silent lesions, and advances in surgical and peri-operative care, which have decreased the mortality rate of pancreatectomy procedures from 20-30% in the 1980s to below 5% in 'very high-volume' institutions.

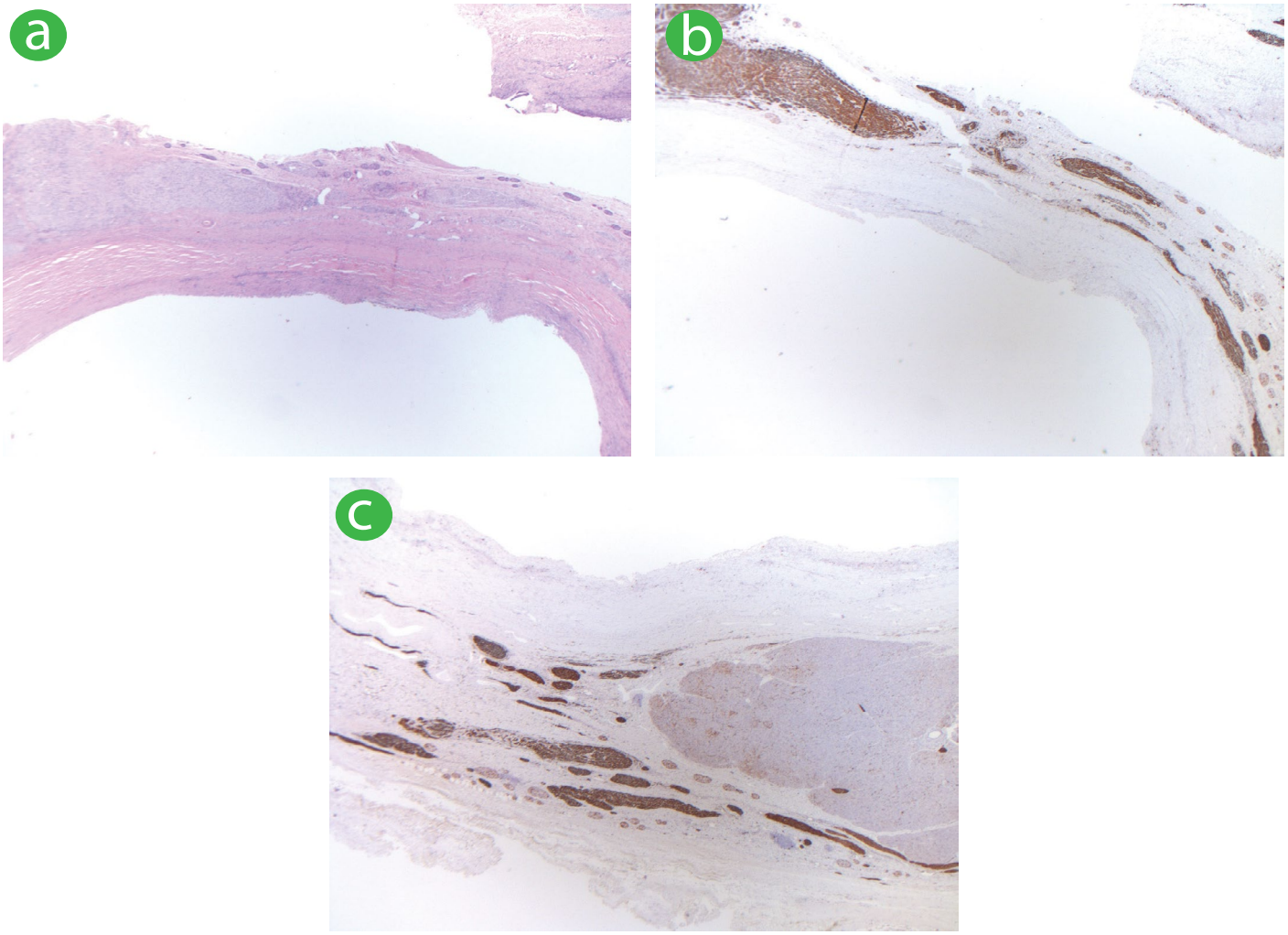

Figure 3. Striking neuronal hyperplasia was present in the pancreatic parenchyma adjacent to the cyst (**3a**; H&E, x16,), characterised by a proliferation of bundles of S100-protein positive spindle cells in a plexiform pattern (**3b**; S100, x16). Neuronal hyperplasia was also present in the pancreatic parenchyma remote from the cyst (**3c**; S100, x16).

A recent review by Freeny and Saunders highlights the limitations of cross-sectional imaging in evaluating cystic pancreatic lesions, particularly those <3 cm in size. Specific imaging features may be absent in 13-88% of cases and imaging features of benign cysts (e.g. lymphoepithelial cysts or serous cystadenomas) may overlap with malignant or potentially malignant lesions, such as mucinous cystic neoplasms [2, 3]. As such, many of these lesions are excised for definitive pathological evaluation.

Pancreatic cystic lesions can be classified histologically based on the presence/absence of an epithelial lining, and based on the type of cyst lining seen microscopically. We focus on the differential diagnosis of squamous-lined cysts of the pancreas.

Lymphoepithelial Cysts

Lymphoepithelial cysts (LECs) of the pancreas are rare (0.5% of all pancreatic cysts), benign, non-neoplastic, cystic lesions seen predominantly in males, in the fifth to sixth decades of life [4, 5]. The most common symptom at presentation is abdominal pain. Other symptoms include anorexia, weight loss, nausea, vomiting, fatigue, back pain, fever and chills. Many cases are detected during radiological work-up for other diseases.

The etiopathogenesis of LECs of the pancreas is not known, but they have been hypothesized to develop from ectopic pancreatic tissues in a peri-pancreatic lymph node, aberrant positioning of branchial cleft cysts at embryogenesis (because the two lesions histologically resemble one another), or squamous metaplasia in an intra-pancreatic duct [6, 7]. They do not appear to be associated with any autoimmune conditions (e.g. Sjogren disease), human immunodeficiency virus infection, lymphoma, or carcinoma, all of which have been documented to occur in the salivary gland counterpart.

Pancreatic LECs may occur in any part of the pancreas [6]. The cyst contents are mostly composed of cheesy/caseous-appearing keratinaceous debris, but may be clear and serous in some cases. LECs are often round and have a well-defined wall that is sharply demarcated from the adjacent pancreatic parenchyma and surrounding adipose tissue. In fact, many cases appear to be peri-pancreatic rather than intra-pancreatic [4].

Histologically, these thin-walled, unilocular or multilocular cysts are lined by well-differentiated, stratified squamous epithelium, with or without prominent keratinization. In some areas, the lining may appear more transitional, and in other areas, the lining is flat, cuboidal or focally denuded.

Sebaceous differentiation and mucinous cells are exceedingly rare, and if present, are very focal [4, 8, 9, 10, 11]. The presence of a significant sebaceous or prominent mucinous component should favor the diagnosis of a dermoid cyst [4].

The squamous epithelium is typically surrounded by a band of dense lymphoid tissue, composed of mature T-lymphocytes with intervening germinal centers composed of B lymphocytes, which may be abundant in some cases. The lymphoid tissue may be immediately adjacent to the epithelium, or there may be a band of fibrous tissue separating it from the epithelium. In some areas, the lymphoid tissue is exuberant but interrupted by complex invaginations of the epithelium, imparting a papillary appearance [4]. Solid lymphoepithelial islands, comprising clusters of epithelial cells admixed with lymphocytes, may be present rarely [4].

Although elevated cyst fluid carcinoembryonic antigen (CEA) levels support the diagnosis of a mucinous neoplasm, many LECs have also been shown to have increased CEA levels [11]. The microscopic differential diagnosis of LECs is mainly with dermoid cysts, epidermoid cysts in intra-pancreatic accessory spleens (ECISs), lymphangiomas and pseudocysts, which share various clinical and pathological features. Dermoid cysts and ECISs tend to be detected in younger age groups than LECs. There is no gender predominance in dermoid cysts and ECISs, whereas LECs are seen more often in men. The presence of mucinous cells and especially respiratory-type mucosa would be more indicative of a dermoid cyst. The presence of splenic red pulp is diagnostic of ECISs. Unless there is extensive sebaceous differentiation, hair follicles, respiratory mucosa, or other teratomatous elements, squamous-lined cysts with a subepithelial rim of dense lymphoid tissue of non-splenic type should be classified as LEC.

There has not been any reported cases of LEC recurrences or progression into lymphoma or carcinoma.

Squamoid Cyst of Pancreatic Ducts

Squamoid cyst of pancreatic ducts (SCOP) is a recently recognized benign cystic lesion in the pancreas, in which cystically dilated pancreatic ducts are lined by squamous/transitional epithelium without keratinization [12]. It is thought that these lesions represent localized cystic dilatation of the native ducts rather than de novo cyst formation [13, 14, 15].

Microscopically, these lesions have abortive septae, irregular contours, are found lying within compact acinar tissue, and appear to be transforming from intercalated ducts, often showing adjacent tightly packed clusters of ducts with similar morphology. They are uniloculated cysts, with variable epithelial lining, composed of flat, transitional epithelium or simple stratified squamous epithelium, lacking a granular layer, parakeratosis and keratinization [16]. Tall-columnar mucinous cells or acinar cells are not evident. Neither acute nor chronic inflammation is a feature of this lesion.

These cysts typically contain distinctive acidophilic acinar secretions that form concretions, more evident in medium-sized examples, confirming their communication with the acinar system, and suggesting a localized obstruction in their pathogenesis.

Immunohistochemically, nuclear p63 expression is present in all cases, a finding that is not seen in any normal component of pancreas or in non-squamous cystic lesions of the pancreas. Both MUC1 and MUC6 (markers present in intercalated duct cells) are expressed in larger lesions. GLUT-1 (consistent marker of serous adenomas) is negative [14]. Cytokeratin expression profiles are that of pancreatic ducts, showing CK7 and CK19 positivity and lacking CK20.

The main differential diagnosis of squamoid cysts of pancreatic ducts is with other squamous-lined cysts of the pancreas. SCOPs lack the underlining lymphoid band or the splenic-type tissue characteristic of lymphoepithelial cysts and epidermoid cyst of intra-pancreatic accessory spleen, respectively. They do not show adnexal-type elements (sebaceous glands, hair, etc.) that are seen in dermoid cysts. Incidental squamous metaplasia may also be seen in otherwise unremarkable ducts with normal caliber and lumen size of uninjured pancreata, characterised by a uniform lining of multilayered transitional/squamous cells.

Squamoid Cystosis of Pancreatic Ducts:

Foo and colleagues reported a case of multifocal cystic dilation and squamoid metaplasia of the distal pancreatic duct system, which they suggest represents an extreme variant of SCOP, which they termed squamoid cystosis of pancreatic ducts. They state that the distinction of squamoid cystosis of pancreatic ducts from squamoid cyst of pancreatic ducts was on the basis of the wide extent of the former. In their report, marked chronic pancreatitis around the involved ducts and a small traumatic neuroma near the junction between the affected and unaffected pancreatic parenchyma were present [13].

Epidermoid Cysts within Intra-Pancreatic Accessory Spleen

Epidermoid cysts within intra-pancreatic accessory spleen (ECISs) are very rare non-neoplastic true cysts and they occur almost exclusively in the tail of the pancreas where accessory spleens are not too uncommon [6, 17, 18, 19]. They are seen in young adults, in the second to third decades of life, occurring equally often in men and women [6].

Several hypotheses regarding histogenesis have been postulated [6]: the cyst originates in a pancreatic duct protruding into an intra-pancreatic accessory spleen; it arises from a mesothelial inclusion with subsequent squamous metaplasia; the lesion represents a by-product of a teratoma or an inclusion of fetal squamous epithelium [20, 21].

These well-marginated multi- or uni-locular cysts may contain serous fluid, with a variable amount of keratin [6]. Histologically, the cysts are lined by attenuated squamous

epithelium, usually non-stratified, surrounded by normal-appearing splenic tissue. In some cases, the cyst lining may be partly mucinous [17].

No reports have described malignant change in an epidermoid cyst arising from an intra-pancreatic accessory spleen [6].

Dermoid Cysts

Mature cystic teratomas are neoplasms of germ cell origin, with the capacity to generate tissues from all of the three germ layers (ectoderm, endoderm, and mesoderm) [22]. They are thought to arise from the embryonic inclusion of skin, at the time of neural groove closure, therefore they are typically found along the midline [22]. They are exceedingly rare in the pancreas [17, 23, 24], and are predominantly monodermal teratomas with only ectodermal derivatives, thus being referred to as dermoid cysts [17]. They are reported predominantly in young adults, in the second to third decades of life, without gender preference [25]. Clinical presentation of pancreatic dermoid cyst is non-specific. Complaints at presentation include abdominal pain, back pain, nausea, vomiting, anorexia, weight loss, fatigue and fever and some cases can be diagnosed during a work-up for other diseases [22].

Dermoid cysts of the pancreas may occur in the pancreatic head, body or tail [25]. Macroscopically, they can have solid and cystic areas and the cyst contents appear pasty, 'cheesy' or 'caseous', comprising keratinous and sebaceous secretions; rarely the contents may be clear and serous. Hair and teeth may also be present.

Dermoid cysts of the pancreas are true cysts and they are similar to teratomas seen in other sites. The wall typically consists of stratified squamous epithelium and underlying connective tissue, although some are composed predominantly of epidermal elements, making the distinction from LECs difficult. The presence of sebaceous glands or hair follicles is more typical for dermoid cysts. Mucinous epithelium, respiratory-type mucosa, and underlying lymphoid tissue, cartilage and fat may also be present [6, 22].

Dermoid cysts are benign neoplasms, although a small percentage of mature teratomas may develop into malignant forms: therefore, thorough sampling of the lesion is necessary to exclude the presence of immature foci [25]. However, all reported pancreatic teratomas have been of mature type (benign) [25].

Malignant Cystic Lesions

Pure squamous cell carcinoma (SCC) of the pancreas is very rare, with a reported incidence of 0.5% of all pancreatic carcinomas, and occasionally presents as a cystic mass [26, 27, 28]. Primary SCC of the pancreas is typically diagnosed only after other primary sources have been excluded by appropriate diagnostic tests (to rule out metastatic SCC to pancreas, which may also present as a cystic mass), and only after the presence of a glandular component has been ruled out (excluding adenosquamous carcinoma of pancreas) [28].

Management

A pancreatic cyst that has been surgically completely excised and is one of the benign squamous-lined cysts described in this review requires no further treatment. A cystic squamous cell carcinoma of the pancreas requires further clinical and radiological correlation to determine if the tumor is a primary pancreatic tumor or a metastasis from a primary squamous cell carcinoma elsewhere. Patients with a malignant tumor require an oncological opinion regarding adjuvant therapy.

Neuronal Hyperplasia

Finally, an unusual feature of our case is the presence of prominent neuronal hyperplasia in the pancreatic parenchyma adjacent to the cyst, which has not previously been reported in association with a pancreatic cyst. The prominence and arrangement of the neuronal hyperplasia simulated a plexiform lesion. Such proliferation is not usually seen in pancreata, even in the presence of chronic pancreatitis, and the possibility that this is a forme fruste of neurofibromatosis cannot entirely be excluded.

Foo *et al*. reported a case of a granular cell traumatic neuroma arising adjacent to squamoid cystosis of pancreatic ducts. In their case, the traumatic neuroma was associated with morphological features of chronic pancreatitis in the adjacent pancreatic parenchyma [13]. Our case of neuronal hyperplasia simulating a plexiform lesion is distinct from the case described by Foo and colleagues.

Neuromatous hyperplasia has been described as a common occurrence in the appendix, sometimes leading to partial or complete obliteration of the appendix [29]. Olsen *et al*. postulated that previous, possibly minimal, attacks of inflammation may induce a proliferation of neurogenous tissue in the appendix, resulting in the neuromatous hyperplasia appreciated histologically. Neuromatous hyperplasia has also been described in the submucosal and myenteric plexuses of the small and large colons of some Crohn's disease patients with chronic colitis [30] and in the left colons of patients with lymphogranuloma venereum [31]. In addition, neuronal hyperplasia has been reported in the submucosa of haemorrhoidectomy specimens [32]. It has also been reported in gallbladders, either in the connective tissue beneath the epithelium or in the outer part of the muscularis, often associated with cholesterolosis [32].

We propose that, in our case, the extensive inflammation with granulation tissue formation and fibrosis associated with the cyst, induced proliferation of neurogenous tissue in the pancreas, resulting in the neural hyperplasia appreciated histologically.

CONCLUSION

Cystic pancreatic lesions are increasingly being detected incidentally due to the increased use of cross-sectional

imaging. Most cystic lesions are non-infiltrative, and are thus amenable to resection, and are biologically curable, and therefore undergo resection. As a consequence, there has been a remarkable increase in the exposure of surgical pathologists to these lesions.

Squamous-lined cysts of the pancreas represent a rare group of true cysts. The importance of these lesions is in their distinction from other cystic neoplasms, especially mucinous cystic tumors and it is usually not possible to make this distinction pre-operatively. Consequently, thorough pathological examination with subsequent accurate classification is imperative.

Longitudinal follow up of our current patient and any future case reports/case series would be helpful.

Conflicts of Interest

The authors have declared that no conflicts of interest exist.

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