CLINICAL CASE

Reactive nodular fibrous pseudotumor: A first report of gastric localization and clinicopathologic review

Pseudotumeur fibreuse nodulaire réactionnelle : à propos d’un premier cas de localisation gastrique et revue clinico-pathologique

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Summary Reactive nodular fibrous pseudotumor (RNFP) of the gastrointestinal tract is a distinct benign lesion, which could originate from a reactive proliferation of multipotential subserosal cells. This is the first case to be reported in the stomach. It was fortuitously discovered in a 60-year-old man with history of bulbar ulcer and gastritis. Gross examination revealed three lesions in the gastric wall and an adjacent lesion in the lesser omentum. Histologically, lesions were composed of a proliferation of spindle and stellate cells in a dense collagenic hyalinized background containing a mononuclear cell inflammatory infiltrate with numerous lymphoid aggregates and plasma cells with perivascular disposition. Immunohistochemistry showed staining for cytokeratins (AE1/AE3), vimentin and smooth muscle actin, without staining for the neurofilament and S100 proteins, synaptophysin, calretinin, CD117 (c-kit), CD34, desmin, caldesmon or anaplastic lymphoma kinase (ALK-1). Complete excision was performed, and no evidence of disease was found 4 months later. After analysing clinical, morphological and immunohistochemical features of this entity, the main differential diagnoses will be discussed, including calcifying fibrous pseudotumor, which shares morphological characteristics with RNFP, but which immunohistochemistry and the ultrastructural study suggest that it may be a result of another reactive process.

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Résumé La pseudotumeur fibreuse nodulaire réactionnelle (PFN) du tractus gastro-intestinal est une lésion bénigne qui résulterait d’une prolifération de cellules multipotentes sous-séreuses. Nous rapportons un premier cas de localisation gastrique, de découverte fortuite chez un patient de 60 ans aux antécédents d’ulcère bulbaire et de gastrite. L’examen macroscopique mettait en évidence trois lésions de la paroi gastrique et une lésion du petit épiploon. Histologiquement, ces lésions étaient composées d’une prolifération de cellules fusiformes et...
étolées dans un stroma collagène dense et hyalinisé, s’accompagnant d’un infiltrat inflammatoire mononucléé avec de multiples follicules lymphoïdes et des plasmocytes de disposition périvasculaire. L’étude immunohistochimique montrait une expression des cytokératines (AE1/AE3), de la vimentine et de l’actine musculaire lisse, sans marquage pour les protéines S100 et du neurofilament, la calrétinine, la desmine, la caldesmone, anaplastic lymphoma kinase (ALK-1), CD117 (c-kit) et CD34. L’exérèse était complète. On ne constatait aucune récidive après un suivi de quatre mois. Après avoir analysé les aspects cliniques, morphologiques et immunohistochimiques de cette entité, nous discuterons des diagnostics différentiels et en particulier de la pseudotumeur fibreuse calcifiante. Celle-ci est morphologiquement proche de la PFNR, mais, d’après ses caractéristiques immunohistochimiques et ultrastructurales, pourrait résulter d’un processus réactionnel distinct.

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Introduction

Benign mesenchymal tumors and pseudotumors of the gastrointestinal tract include various lesions with different prognoses. Reactive nodular fibrous pseudotumors (RNFP) of the gastrointestinal tract and mesentery were defined in 2003 by Yantiss et al. [1]. Only 16 cases have been described [1—5]. The clinical, radiological and pathological features of a first case in the gastric wall are reported.

Case report

A 60-year-old man with history of duodenal bulbar ulcer associated with antral gastritis and autoimmune polyendocrinopathy (including hypothyroidia and adrenal insufficiency), underwent thoracoabdominal computed tomography (CT) scan for polycytemia to exclude a paraneoplastic syndrome. There were no clinical symptoms. CT scan (Fig. 1) revealed one nodular lesion of the anterior wall of the gastric antrum and a lobulated lesion of the distal gastric antrum. Both seemed to be exoluminal. These tumors were spontaneously isodense, with progressive contrast enhancement. Moderate hypointensity on T1 and significant hypointensity on T2-weighted images were noted. Due to these unspecific radiological features, which could suggest a gastrointestinal stromal tumor (GIST), the lower two thirds of the stomach and part of the lesser and greater omentums were resected.

Pathologic examination showed one lesion of the wall of the gastric antrum, 2.2 cm in diameter, and three adjacent lesions close to the antropyloric junction (corresponding to the lobulated tumor seen on CT scan), measuring between 1.9 to 2.1 cm, one of which was located in the lesser omen tum (Fig. 2a). The latter had stellate borders and the others were well-defined but not encapsulated. Lesions on the cut section were grayish white (Fig. 2b) and very firm. The lesion in the lesser omentum had irregular borders with thick collagenic bands reaching the mesothelium (Fig. 3). The three other lesions had well-defined borders, and seemed to have developed from a subserosal site, with one also involved in the deep muscularis propria. All were composed of a dense collagenic hyalinized stroma, containing a sparse mononuclear cell inflammatory infiltrate, made of lymphocytes and plasma cells with a perivascular disposition, some mast cells

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Figure 3  a: unencapsulated lesion located in the subserosa, with well-defined borders; b: the lesion situated in the lesser omentum has irregular borders, with thick collagenic bands reaching the mesothelium (HES).

Discussion

Sixteen cases of RNFP have been reported so far, including five women and 11 men ranging from 1 day to 72 years of age. With the present case reported here, the sex-ratio male/female is 2.4, and the mean age is 47-years-old. Among the eight patients with an available medical history, four had a history of abdominal surgery [1,5]. Lesions were asymptomatic, or revealed by abdominal pain, bowel obstruction, haemorrhage or peritonitis. Eleven were unique and five multiple.

The localizations are small bowel (6/16), colon (7/16), vermicular appendix (3/16), mesentery (4/16), omentum (2/16), peripancreatic fat (1/16) and ovaries (1/16). We report the first case to occur in the gastric wall.

There is no detailed radiological description of RNFP in literature. We describe a moderate hypointensity on T1 and a significant hypointensity on T2-weighted magnetic resonance images, associated with progressive contrast enhancement, which could suggest the fibrous composition of RNFP.

Morphological findings were very similar in all cases. Macroscopically lesions were firm or elastic, homogeneous, and white, gray or yellowish tan. The largest lesion measured 10 cm in diameter [3]. Most were nodular, or present with a thickened wall [3] or with cord-like structures [5]. They may be unencapsulated, well-defined, or extend in a scar-like way into the adipose tissue [3]. They often seem to arise from the subserosa, reaching the muscularis propria or submucosa [3], and three cases of transmural extension have been reported [1,4], two associated with ulcerations or perforations [1]. Microscopic examination of RNFP shows a pauci- or moderately cellular proliferation of stellate or spindle cells, in a dense collagenous background, with hyalinization or keloid-like appearance. These cells are scattered, or arranged in poorly-formed, short fascicles. No or few mitoses can be seen. There are no atypical nuclei. Calcifications of concentric hyaline whorls were found in one case [3]. Focal necrosis was described in three cases by Daum et al. [3]. In all cases but one [5], sparse inflammatory cells were present, which are mostly mononuclear lymphoid cells, frequently arranged in lymphoid aggregates. Three lesions also contained giant cells [3,4], around foreign material in two cases [3]. Chatelain et al. [2] described an RNFP developing around an inflamed and perforated duodenal diverticulum. Saglam et al. reported numerous lesions of the ovaries, omentum and appendix associated with endometriosis [4].

Immunohistochemistry (Table 1) shows positive staining for vimentin (15/15), smooth muscle actin (15/17) and specific muscular actin (9/12). Staining for cytokeratins is
irregular. In the Daum et al. series [3], six out of seven cases were positive for cytokeratin AE1/AE3 (AE1/AE3, Neo-Markers), while in the Yantiss et al. series [1] there was no staining for AE1/AE3 (0/5, AE1/3, Signet). In the present case, a strong staining for cytokeratins AE1/AE3 (AE1 + AE3, Dako) was found. These different results could be explained by the use of different antibody clones. Immunoreactivity for CD117 (c-kit) was also inconstant (5/17). All lesions were negative for ALK-1 (0/14) and S100 (0/14). Ultrastructural study was described in four cases [2,3], showing features of a partial myofibroblastic differentiation. Daum et al. did not find any found c-kit exon 9 or exon 11 abnormalities with polymerase chain reaction [3].

There was no evidence of disease after between 10 months and 7 years (0/9) of follow-up. One patient has several remaining lesions, and imaging studies remain unchanged after 26 months [1].

Staining for vimentin and smooth muscle actin, as well as ultrastructural findings suggest a partial myofibroblastic differentiation of stellate or spindle cells. These results associated with the expression of cytokeratins AE1/AE3 found in many cases of RNFP, suggest that RNFP is a prolifer-

ation derived from multipotential subserosal cells, sharing the same morphologic, immunohistochemical and ultrastructural features [6–8].

A history of abdominal surgery, the presence of foreign bodies and the association with endometriosis or inflamed diverticulum found in some cases as well as the presence of sparse inflammatory cell infiltrates suggest that this is a reactive process. Pitt and Haboubi describe reactive hyperplasia of multipotential subserosal cells in chronic gastric ulcers [8], suggesting that our patient may have developed RNFP secondary to gastric inflammation.

Calcifying fibrous pseudotumor (CFP), which shares many similar morphological features with RNFP, has a wide anatomical distribution. It is most often located in soft tissue, but can also occur in the mesentery, omentum and stomach [9–11]. Only eight cases of gastric CFP have been reported [9,11–16]. Whereas all cases of RNFP arise in the subserosa, gastric CFP has presented as a submucosal polypoid mass [9,12–14,16], except in one case [15]. Like RNFP, CFP is relatively well-circumscribed but may occasionally have infiltrative borders [10]. It is composed of a hypocellular spindle cell proliferation within dense stromal collagen, and a lymphocytic and plasma cell infiltrate with lymphoid aggregates, but also contains whorled collagen with numerous psammomatous and dystrophic calcifications [9,10,17]. CFP differs from RNFP in its immunohistochemical features. Contrary to RNFP, CFP is negative for smooth muscle actin and muscle specific actin [9,10,12,14–19], or occasionally shows staining of rare spindle cells [11]. Some cases are positive for CD34 [11,17]. There is no expression of cytokeratin [18,19]. Electron microscopy shows that spindle cells of CFP are consistent with immature fibroblasts [17], which suggests that CFP could be due to a reactive proliferation of fibroblasts, whereas RNFP would be a result of multipotential subserosal cells.

Because of the potential aggressive progression of GIST, it is one of the most important differential diagnoses to be made for RNFP. GISTs are often located in the muscularis propria, while RNFP predominate in the subserosa. They are usually more cellular, and composed of fascicles of epithelioid or plump spindle cells with eosinophilic cytoplasm separated by delicate fibrous septae, within a hyalinized or edematous stroma [20], although some may be collagen-rich and paucicellular. Most GISTs stain strongly for CD117, and edematous stroma [20], although some may be collagen-rich and paucicellular. Most GISTs stain strongly for CD117, more variably for CD34 and sometimes for PS100. Inflammatory fibroblastic tumors and related lesions have a strong tendency to recur locally, and must also be distinguished from RNFP. They typically appear in childhood or young adulthood with systemic manifestations. They are hypercellular tumors with loosely arranged fascicles of ALK-1 positive spindle cells with some cytologic atypia, frequent mitoses and abundant eosinophilic cytoplasmic and nuclear stroma containing abundant lymphoplasmocytic infiltrate [21]. Intra-abdominal fibromatosis contains long, regular fascicle of spindle cells, and slit-like or ectatic vascularule [22]. Sclerosing mesenteritis contains thick collagen bands that dissect through lobules of fat, which may contain fat necrosis [23]. Although schwannoma can be located in the stomach, it is situated mainly in the muscularis propria. Like RNFP, most contain peripheral lymphoid aggregates, and sometimes collagenous tissue stroma, but schwannoma are more cellular, with bipolar
spindle cells staining for S100 protein [24]. Inflammatory fibroid polyps (Vanek’s tumor) arise from the submucosa or mucosa and present as polypoid lesions. Histologically, it is described as a localized proliferation of spindle and stellate cells arranged in an onion-skin like concentric formation around blood vessels and mucosal glands, accompanied by an inflammatory reaction. Contrary to RNFP, the proliferating cells stain for CD34 [25]. Finally, sarcomatoid carcinoma is composed of fusiform cells positive with vimentin and cytokeratin, but the constant presence of atypical nuclei helps distinguish it from RNFP.

### Conclusion

RNFP is a benign reactive lesion of the gastrointestinal tract that can be an incidental finding, or associated with abdominal pain, bowel obstruction, haemorrhage or peritonitis. Localization, morphological, immunohistochemical and ultrastructural features suggest that RNFP is a proliferation derived from multipotential subserosal cells. This diagnosis should be kept in mind by both clinicians and pathologists when confronted with unique or multiple nodular subserosal fibrous lesions of the gastrointestinal tract, especially in case of previous abdominal surgery. Indeed, RNFP does not recur after simple excision, unlike some of its main differential diagnoses, such as GIST, inflammatory myofibroblastic tumor and intra-abdominal fibromatosis.

### Conflicts of interest

None.

### References


