

Case Report

Gangliocytic paraganglioma of the appendix with features suggestive of malignancy, a rare case report and review of the literature

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Abstract: We report a case of appendiceal paraganglioma in a 40 year old female who presented with acute appendicitis and underwent laparoscopic appendectomy. To the best of our knowledge this is the first reported case of appendiceal gangliocytic paraganglioma with features suggestive of malignancy in the modern literature. Van Eeden S. et al. reported the first case of appendiceal paraganglioma in a 47 year old man who also presented with acute appendicitis. The appendectomy specimen showed a distended appendix with thickened wall, and a 1.3 cm mucosal based yellow lesion. Microscopically this lesion was centered in the submucosa and consisted of three different cell types: (a) epithelioid cells with pale eosinophilic finely granular cytoplasm containing bland oval nucleus with stippled chromatin, that form solid nests lying in a trabecular pattern and in formations reminiscent of 'Zellballen' as seen in paragangliomas (b) second type cells have large vesicular nuclei with prominent nucleoli and abundant cytoplasm that are scattered singly, (c) third type cells with bland elongated nuclei form broad fascicle and envelop the epithelioid and ganglion cells. Immunohistochemical analysis showed the epithelioid cell nests immunoreactive for synaptophysin and the ganglion-like cells and spindle Schwann cells to be immunoreactive for S100 protein, whereas all three cells populations were negative for CAM5.2 and Pancytokeratin. We do believe that an accurate diagnosis of Gangliocytic paraganglioma (GP) of the appendix was rendered, detailed microscopic examination of doubled hematoxylin and eosinophil stained sections as well as the immunohistochemical phenotype of the three components have been undertaken to confirm the diagnosis of GP.

Keywords: Appendix, gangliocytic paraganglioma, carcinoid, immunohistochemistry

Introduction

Gangliocytic paraganglioma (GP) is a rare tumor which occurs nearly exclusively in the second portion of the duodenum [1-3]. The lesion was first described by Dahl et al. in 1957, and further characterized as a benign nonchromaffin paraganglioma by Taylor and Helwig in 1961 [4, 5]. In 1971 the term "gangliocytic paraganglioma" was established by Kepes and Zacharias, recognizing the features in common between both paraganglioma and ganglioneuroma [6]. The pathognomonic features of this neoplasm are the identification of three distinct cellular elements: spindle cells, epithelial cells, and ganglion cells. Phenotypical analysis by immunohistochemical examination is considered

crucial step in the diagnosis of GP and immunohistochemically these tumors stain positive for a variety of markers as was shown in the current case. Such markers include those mentioned above as well as neuron-specific enolase, pancreatic polypeptide, somatostatin, myelin basic protein and neurofilament proteins [7-9]. Generally these tumors have benign clinical course, although rarely they may recur or metastasize to regional lymph nodes [10-12]. To date, the histological features predicting malignant potential of GP have not been well-defined. However, as it is observed in the current case it has been suggested that the presence of nuclear pleomorphism, mitotic activity and infiltrative margin, raises the concern for aggressive behavior [13].

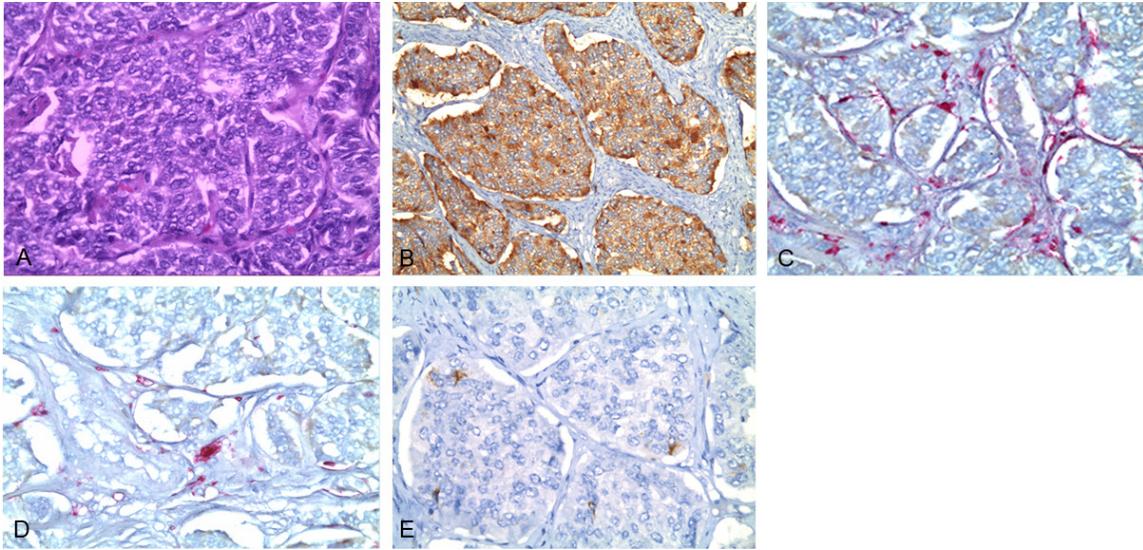


Figure 1. A. H&E stain shows nests of epithelioid cells surrounded by thin strands of spindle cells reminiscent of “Zellballen” formation (100 x); B. The epithelioid tumor nests show diffuse immunoreactivity for synaptophysin (100 x); C. S100 immunostains highlights the spindle cells surrounding the epithelioid nests (100 x); D. s100 immunostain highlights a ganglion-like cell among the epithelioid nests (200 x); E. shows negative immunoreactivity of the tumor cells to Cam 5.2 and AE1/AE3 (200 x).

Material and methods

The following case was evaluated and reported in accordance with the University of South Florida’s Institutional Review Board Policy #311.

Case report

Here we report a case of appendiceal paraganglioma in a 40 year old female who presented with signs and symptoms of acute appendicitis and underwent laparoscopic appendectomy. To the best of our knowledge this is the first reported case of appendiceal gangliocytic paraganglioma with features suggestive of malignancy in the modern literature. Van Eeden S. et al. [1] reported the first case of appendiceal paraganglioma in a 47 year old man who also presented with signs and symptoms of appendicitis.

Results

Pathological evaluation

The surgical specimen consisted of an intact distended appendix with thickened wall that was fixed in 10% buffered formalin. A solid submucosal based yellow 1.3 cm lesion was identified. Sections of paraffin-embedded tissue were prepared and stained with hematoxylin and eosin (HE) double stain for light microscop-

ic observation. Histological examination showed an un-encapsulated submucosal lesion that had an infiltrative margins with extension through the muscularis propria to penetrate the visceral peritoneum. Tumor cell necrosis was present, comprising approximately 30% of the tumor mass, the mitotic count was 3 per 10 high power fields. The tumor is composed of three cells subtype including; epithelioid cells with pale eosinophilic finely granular cytoplasm bland oval nucleus with stippled chromatin, forming solid nests lying in a trabecular pattern in formations reminiscent of ‘Zellballen’ as seen in paragangliomas and they were surrounded by spindle cells (**Figure 1A**), and rarely seen single ganglion-like cells with polyhedral amphophilic cytoplasm with round nucleus with prominent nucleolus identified in the submucosa and among the epithelioid nests. The synaptophysin stain showed positivity in the epithelioid cells (**Figure 1B**). The spindle cells and the ganglion-like cells stained with S100 (**Figure 1C** and **1D**). AE1/AE3.CAM5.2 was negative in all three cell populations (**Figure 1E**). The proliferative index study Ki-67 showed approximately 1% nuclear staining.

Discussion

Gangliocytic paraganglioma has three characteristic histological components: epithelioid,

ganglion and spindle cells, the proportion of the three cell types varies in each tumor, but each component shows characteristic immunohistochemical staining similar to those observed in the present case. There are several entities that were referred to in the differential diagnosis of the histopathological examination of the present case including carcinoid tumor, paraganglioma, and ganglioneuroma. In general, most GP are benign with innocuous course and are amenable to local resection [3]. However, there are rare reports of recurrences, lymph node involvement and distant metastasis [11, 15-18]. Okubo [26], indicated in 2011 literature survey that the rate of lymph node metastasis of duodenal GP is 6.9% (12/173 cases), and Wong A *et al* [20] suggested that approximately 5% of gangliocytic paraganglioma demonstrate malignant behavior. In a search of the recent literature we have identified fourteen cases with malignant features, thirteen presented with lymph node involvement while one with distant metastasis to the liver and bone. All are GP cases of the duodenum or ampulla of Vater and one case was GP of the head of the pancreas. Up to date there are no definitive histologic features for predicting the malignant potential of GP. However, Witkiewicz. *et al.* [12] suggested that the presence of nuclear pleomorphism, mitotic activity and infiltrative margins may raises the concern for an aggressive course. The prognostic role of immunohistochemistry in neuroendocrine tumors such as pheochromocytoma [23, 24], thymic and lung neuroendocrine tumors [21] has been investigated claiming that the expression of bcl-2 and p53 which are two proteins that control apoptosis, correlated with malignant behavior. There is scarcity in studies investigating the prognostic utility of P53 and/or bcl-2 limited GP, but we like to emphasize that the rarity of the tumor is a factor.

Therefore, we examined the pattern of P53 and bcl-2 expression in the present case. Unfortunately, in contrary to the reactivity of p53 in adenocarcinoma ex goblet cells carcinoid of the appendix which is rare neuroendocrine tumor, moreover despite the presence of worrisome histomorphological features the tumor cells showed negative reactivity for both markers. Our results are in concordance with Okubo *et al* [27] who reported a case of duodenal GP with node involvement despite lack of

bcl-2 and p53 expression. Therefore, it seems that the immunohistochemical studies have limited prognostic utility in GP. We like to emphasize that our patient on follow-up did not show any evidence of recurrence or abnormal imaging studies.

In the modern literature we identified single previous report of gangliocytic paraganglioma of the appendix [28]. However, more than 50 years ago Masson [29] reported a case of neuro- carcinoid in the appendix with histomorphological features similar to GP and we agree with Van Eeden S. [28] that Masson can be considered the first to describe GP of the appendix. Gangliocytic paraganglioma has generally been regarded as a neuroendocrine tumor; its origin is unclear and remains a matter of debate with no uniform consensus. There are several proposed theories in the literature regarding the origin/pathogenesis of GP. Considering our finding of gangliocytic paraganglioma of the appendix; we are inclined to agree with Perrone T. *et al.* theory that reconciles the combination of endocrine, ganglion and spindle cells identified in a single tumor. In a study examining the immunohistochemical and ultra structural features of gangliocytic paraganglioma Perrone T, proposed that gangliocytic paragangliomas GP is hyperplastic or neoplastic proliferation of endodermally derived epithelial cells, and neuroectodermally derived ganglion cells and Schwann cells arising from Van Campenhout's sympathetico-insular complexes [14, 30]. These endodermal-neuroectodermal complexes can be found in the appendix of mammalian embryos. On the other hand, Burke AP [2] proposed that GP is a hamartoma/choristoma rather than true neoplasm. However, there are several reports of metastatic GP to the regional lymph nodes and recurrence [11, 15-18], supporting GP true neoplastic nature.

We like to emphasize that the surgical therapy of GP should not be limited to local resection, as disease recurrence, lymph node involvement and rarely distant metastasis may occur, particularly with the lack of discerning prognostic markers. Local resection, with no lymph node dissection could be a factor in underestimating the malignant potential of GP. Moreover, there is a high rate of gangliocytic paragangliomas exceeding the submucosal layer [13], a risk factor for lymph node metastasis, which

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makes CT/MRI particularly important. Additionally, we need larger studies with longer follow-up investigating the Ki-67, bcl-2 and p53 as prognostic markers in this neoplasm.

Disclosure of conflict of interest

None.

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