Case Report

Colonic gastrointestinal stromal tumor: A diagnostic dilemma on cytology

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ABSTRACT

Gastrointestinal stromal tumors (GIST) is mesenchymal tumors arising from the interstitial cells of Cajal (pace maker cells) of the gastrointestinal tract (GIT). Stomach is the most common site (60-65%) of these tumors. Large intestine and rectum constitute only 5-10% of GIT tumors. Pre-operative diagnosis helps in the management of this tumor as it responds well to c-kit inhibitors. The cytological diagnosis of GIST is characteristic, however, associated with many pitfalls leading to erroneous diagnosis. Morphological resemblance is seen with other spindle cell and epithelioid cell tumors. The differentiation between high grade and low grade GISTs is described but not reliable. Cytology combined with cell block and Immunocytochemistry helps in making a confident diagnosis. Here we present colonic GIST diagnosed as GIST on cytology and confirmed on histopathology. We report this case to describe the cytological features of GIST and pitfalls in the cytology.

Key words: Colon, gastrointestinal stromal tumor, interstitial cells of Cajal

INTRODUCTION

Gastrointestinal stromal tumors constitute 0.1-3% of gastrointestinal tumors (GITs).[1] GISTs are mesenchymal tumors having a submucosal location. Stomach is the most common site for GIST followed by the small intestine (20–25%), colon and rectum (5%), and esophagus (<5%).[2] GISTs express c-kit proto-oncogene, are immune-reactive for CD-117 and they respond to c-kit inhibitors.[3] Pre-operative diagnosis on cytology is helpful in the management of the GIST. Cytological examination helps in the pre-operative diagnosis. However, there are various pitfalls in diagnosis of GIST on cytology. Close resembles with smooth muscle tumors, nerve sheath tumors, granulation tissue, epithelial tumors, and inability to predict the long term behavior of tumors are some of the pitfalls. Cytology combined with cell block preparation and Immunocytochemistry are helpful in making a confident diagnosis pre-operatively.

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CASE REPORT

A 55-year-old male patient presented with pain in right lumbar region and altered bowel habits for 2 months. General physical examination was within normal limits. On abdominal examination, an ill-defined firm mass was detected in right hypochondrium. Ultrasonography revealed a soft-tissue mass involving the ascending colon. Ultrasound guided fine-needle aspiration (FNA) was performed from the colonic mass.

Cytological smears revealed pleomorphic cells lying singly. Individual cells revealed high nucleo-cytoplasmic ratio, eccentrically placed nuclei, irregular nuclear membrane, hyperchromatic to granular chromatin, and 1-2 conspicuous nucleoli [Figure 1a]. The cytoplasm was abundant, had irregular cell borders, fine vacuolated, and showed cytoplasmic protrusions [Figure 1b]. On the basis of cyto-morphological features, a diagnosis of malignant mesenchymal tumor - colonic mass was given. A right hemicolectomy was performed. Grossly, an ulcerated growth was seen on the mucosal surface. Microscopic examination revealed spindle shaped tumor cells forming short fascicles in the submucosa [Figure 1c]. The growth extended up to the serosa. Areas of necrosis were seen. The mitotic count was 5 mitotic figures/50 high power field (hpf). Immunohistochemistry was performed for

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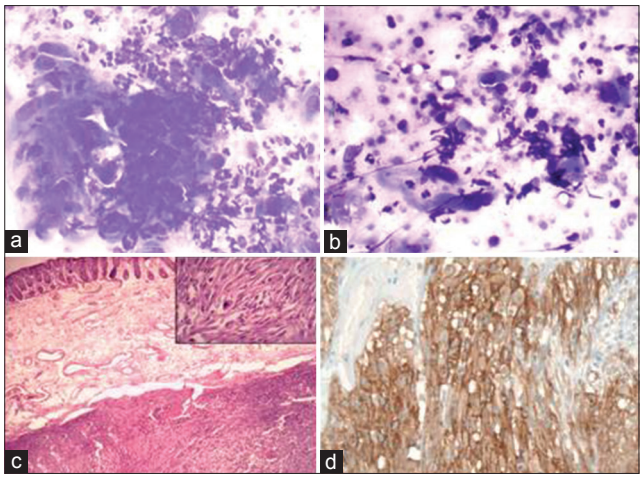

Figure 1: (a) Cytological smears were cellular showing pleomorphic cells with high N/C ratio, eccentric nuclei, hyperchromatic to granular chromatin, and conspicuous nucleoli (Giemsa, ×10). (b) The cytoplasm was abundant, had irregular cell borders, fine vacuolated, and showed cytoplasmic protrusions (Giemsa, ×40). (c) The tumor cells extending from submucosa to serosa, spindle shaped (inset) cells forming short fascicles having eosinophilic cytoplasm, vesicular nucleus and prominent nucleolus (H and E, ×10 and × 40). (d) The spindle cells are immunoreactive for CD-117

desmin, S-100, CD-34 and CD-117. The tumor cells were reactive for CD-117 (cytoplasmic and nuclear) [Figure 1d] and CD-34. Based on the histopathologic features and immunohistochemistry, a diagnosis of malignant GIST– ascending colon was given.

DISCUSSION

Gastrointestinal stromal tumors accounts for only 0.1-3% of all GI neoplasms, but, simultaneously, they are the most frequent mesenchymal lesions of the gastrointestinal tract. GISTs are frankly malignant in 10–30% of cases and cause mortality in 2% of cases.[2] Invasion of adjacent structures or metastases may be present. Metastasis to the ascitic and pleural fluid are also on record. Clinically, most patients present with an abdominal mass, pain and melena. GISTs are believed to arise from interstitial cells of Cajal. These cells express CD-117 (c-kit) antigens. CD-117 is sensitive (79-86%) and relatively specific for GIST. Criteria to predict their tumor behavior include size, necrosis, and mitotic rate as suggested by Miettinen and Lasota[4]. A mitotic count above 5/50 hpf and size above 2 cm is associated with an increased rate of progressive disease and increased risk of metastasis. Primary omental or mesenteric localizations are rare; in such cases the correct term is extra-GIST.[2] GIST has no preference for gender; its peak incidence is between 40 and 70 year, with a broad age distribution.[5] These tumors do not usually involve the mucosa, but commonly originate in the wall of the GIT tract.[6] They represent a morphologically diverse group of neoplasms that display features of smooth muscle and neural differentiation. Each cell possesses a single elongated nucleus with squared-off ends. Their eosinophilic cytoplasm, at times with a perinuclear vacuole, shows no evidence of specific differentiation. Less often, tumors may be composed completely of polygonal neoplastic cells with better defined borders and centrally positioned ovoid nuclei called epithelioid GIST. A single tumor may show both spindled and epithelioid cells.

Gastrointestinal stromal tumors represent a distinct clinicopathologic entity that is characterized by genetic mutations in the c-kit proto-oncogene.[7] Before introduction of endoscopic ultrasound (EUS)-guided FNA biopsy, most of the GISTs were diagnosed by either endoscopic biopsy or surgical resection due to their submucosal or intramural location. Recent studies have shown that EUS combined with FNA cytology appears to be of great value in the evaluation of intramural lesions of the GIT tract, especially GISTs.[8] In practice c-kit inhibitors have become available for the treatment of GISTs, hence the pre-operative diagnosis of these tumors has gained importance.

The cytomorphological features shows only few to moderate numbers of neoplastic cells. They may be dispersed as isolated elements or present as small to large clumps. These clumps may be associated with extracellular matrix material. Each cell is spindle to ovoid in shape, has high N/C ratio. The cells contain single ovoid nucleus with blunt ends. The staining intensity of chromatin is variable. It is usually granular with even distribution. The nucleoli are inconspicuous, cytoplasm is cyanophilic and the cell borders are indistinct. Leiomyoma and leiomyosarcoma (LMS) are very close differential of GIST on cytology. Leiomyoma which is a very common tumor of the GIT is characterized by variable cellularity and are composed of bland spindle cells with abundant cytoplasm often having fibrillary appearance[9]. No atypia, mitosis or epithelioid cells are identified. Wieczorek *et al.*[10] compared the cytology of GIST with that of LMS. The LMS showed three-dimensional, tightly cohesive, sharply marginated syncytia of spindle cells, often with nuclear crush artifact. The cytoplasm/stroma had a distinct wiry, retractile appearance. LMSs more commonly exhibited pleomorphism. Epithelioid cytomorphology, mitoses, and necrosis occasionally were observed in both tumor types. Immunocytochemistry was helpful to differentiate between these two entities. About 100% GIST showed immunostaining with CD-117 and all LMS were immunoreactive for smooth muscle actin.

Other differentials on cytological smears are benign and malignant nerve sheath tumors. These tumors show fibrillar cytoplasm and "wavy" nuclei characteristic of nerve sheath tumors. Metastatic GISTs with epithelioid morphology may cause significant diagnostic difficulty with carcinomas, neuroendocrine tumors, melanoma or even hepatocellular carcinoma.[11] The cytological features of melanoma are loose aggregates or isolated cells, cellular pleomorphism, enlarged nuclei with nucleoli, bi-nucleation,

multi-nucleation, intra-cytoplasmic melanin. Hepatocellular carcinomas show neoplastic cells forming trabeculae and endothelial cells lining the groups. Intra-nuclear inclusions and no bile pigment are important distinguishing features. The distinction of metastatic GIST from other metastatic tumors is important as the former responds well to c-kit inhibitors.

Furthermore, the question of benign versus malignant may be impossible to answer. Vij *et al.*[12] studied the subtle differences between low grade, malignant and metastatic GIST on cytology. Malignant and metastatic GIST was more cellular than the benign GIST. Epithelioid morphology was more commonly seen in malignant and metastatic GIST. The nucleoli were indistinct in low grade GIST and prominent or multiple in high grade GIST irrespective of the cell type. Malignant GIST showed the presence of nuclear inclusions. Ascitic and pleural fluid cytology smears showed the presence of loosely formed aggregates with epithelioid morphology. It was concluded from the study that mitosis was the key morphologic feature that suggested high grade malignant GIST. However, it was difficult to find mitosis in cytological smears since the tumor cells occurred in closely packed

cohesive thick tissue fragments. In their study Li *et al.*[13] they found that mitoses found in resected specimens were seldom found on cytological smears. Very little pleomorphism was found in cytological smears of malignant GIST. Dirty or necrotic background was also not a reliable criterion for differentiating low grade and high grade GIST.

Tamiolakis *et al.*[14] used cell block preparation and immunohistochemistry along with cytological smears for more confident diagnosis. The cell blocks had basophilic appearance and were cellular. Pleomorphism was mild to moderate, mitosis varied from 1 to 10/50 high power field. Nucleoli were indistinct and cytoplasm showed vacuoles. Immunostaining with CD-117 was positive in 100% cell block preparation.

CONCLUSION

Gastrointestinal stromal tumor show a broad morphologic variety, but nuclear pleomorphism by cytology alone, rarely correlates with malignant potential. We were not able to diagnose the mesenchymal tumor as GIST due to unavailability of Immunocytochemistry and lack of material for cell block preparation. An excellent response to c-kit inhibitors warrants pre-operative diagnosis. However, in the appropriate clinical and radiological setting, a confident diagnosis of GISTs can be documented by FNA cytology, cell block and immunocytochemical studies.

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