

Case Report

Gastrointestinal Stromal Tumours - Report of Three Cases and Review of Literature

Deshpande A*, Munshi MM**

Abstract

Three cases of GIST were diagnosed on guided fine needle aspiration cytology. Two cases showed groups and whorls of benign spindle cells with elongated, blunt ended nuclei, which were diagnosed as GIST (probably benign). One case showed more obvious pleomorphism, round nuclei and binucleation. This was diagnosed as GIST (probably borderline/malignant). Although a tentative grading was communicated to the surgeon, it was made very clear that a confident grading cannot be given on cytology because this is based on size, presence of necrosis/haemorrhage and the mitotic count. Although a confident diagnosis of GIST can be made on cytology, we believe that grading should be left to histology.

Journal of Cytology 2007; 24 (2) : 96-100

Key Words : GIST, FNAC.

Introduction

Gastrointestinal stromal tumours (GIST's) are mesenchymal tumours of the gastrointestinal tract arising from interstitial cells of Cajal. Previously believed to be of smooth muscle or neural origin, the concept of GIST has evolved considerably over the past few years especially with the advent of immunohistochemistry (IHC). GIST's are now defined as cellular, spindle cell, epithelioid or occasionally pleomorphic mesenchymal tumours of the GIT expressing CD 34 and CD 117 (c-kit) a product of c kit proto-oncogene.¹ Because of the submucosal or intramural location of this tumour, endoscopic biopsy is often ineffective in making a biopsy diagnosis. Ultrasonography (USG) guided, computed tomography (CT) guided or endoscopic untrasonographically (EUS) guided fine needle aspiration cytology (FNAC) is being increasingly used for the diagnosis of these tumours.^{1,2,4} The cytological features of GIST have been documented and few reports have been supported by immunocytochemistry (ICC).^{1,3,7}

Case Reports

3 cases of GIST diagnosed on fine needle aspiration cytology are presented. All patients were males with ages between 32 and 72 years. The clinical features, radiologic findings, cytologic and histologic findings are summarized in Table 1. Two tumours were aspirated under ultrasonographic guidance and one was aspirated under CT guidance. Aspirations were done with a 22-gauge needle and 20 ml syringe using the standard procedure, and smears prepared. Air-dried smears were stained with May-Grünwald Giemsa stain and alcohol fixed smears were stained with haematoxylin & eosin and Papanicolaou stain. All tumours were resected and subjected to histologic examination. The final diagnosis was correlated with cytology.

Cytological findings: Smears from two cases showed moderate cellularity in a clean background. Spindle shaped cells were seen in cohesive clusters which showed a whorled or palisaded arrangement better seen in alcohol fixed smears (Fig. 1). Single dispersed spindle cells and stripped nuclei were also seen. The cells had a moderate amount of ill-defined cytoplasm which was drawn out at both ends (Fig. 2). Occasional cytoplasmic vacuolation was seen. The nuclei were uniform, oval or cigar-shaped with blunt ends and had a finely granular chromatin without mitoses or nucleoli (Fig. 2). The diagnosis in both cases was GIST (probably benign).

One smear showed loosely cohesive clusters in a myxoid stroma without whorling or palisading (Fig. 3). There were many dispersed single spindle as well as round and polygonal cells with moderate, eosinophilic cytoplasm, plump, oval nuclei, coarse chromatin and

*Associate Professor, Department of Pathology, Indira Gandhi Government Medical College, Nagpur; **Professor, Department of Pathology, Government Medical College, Nagpur.

Received : 18.10.2006 ; **Accepted :** 25.01.2007

Corresponding Author : Dr. Archana Deshpande, 377, Shankarnagar. Nagpur - 440010. Maharashtra.

E-mail: ahdeshpande@dataone.in

Table 1 : Showing details of patients

Case	Age/ Sex	Clinical features	Radiologic findings	Cytologic findings	Intraoperative findings	Gross features	Histologic diagnosis
1	72/M	C/o mass, pain in abdomen and malena. O/E Mass in umbilical region	USG: Diffuse concentric thickening of bowel wall. Large exophytic component involving hepatic transverse colon.	Sheets and single spindle cells, uniform cigar shaped nuclei. No pleomorphism, mitoses.	Large tumour involving duodenum, embedded in the mesentery extending into retroperitoneum.	Globular 10x10x8 cm mass in duodenal loop. C/S-areas of necrosis, haemorrhage, cystic degeneration	Benign GIST
2	70/M	C/o mass, pain in abdomen and malena. O/E Mass in umbilical region and right hypochondrium	USG: Solid, cystic exophytic mass arising from ileum. CT: 9 x 8 x 8 cm solid and cystic lesion arising from ileum causing displacement of sigmoid colon.	Groups of spindle cells with elongated blunt ended nuclei. No pleomorphism or mitosis. GIST	Large tumour mass arising from ileum, fixed to peritoneum, adjoining bowel loops, and anterior abdominal wall.	7 x 6 x 6 cm globular mass on antimesenteric border of small intestine with ulceration of mucosa. C/S fleshy, whorled, appearance.	Benign GIST
3	32/M	C/o Lump, pain in abdomen, O/E mass in epigastrium and umbilical region	USG: 7 x 7 cm solid mass in right hypochondrium and epigastrium with '! vascularity and calcification. CT :Moderately enhancing bulky heterogenous mass in gastrocolic ligament with involvement of liver, gastric antrum and transverse colon.	Few groups of spindle cells with elongated and plump, oval nuclei and moderate amount of cytoplasm. Mild pleomorphism. No mitoses.	Globular tumour arising from antral wall of stomach and attached to omentum	8 x 7 x 6 cm globular mass attached to wall of stomach and omentum. Mass well circumscribed, solid, pale pink on C/S	Borderline GIST

C/o complaints of; CT- Computerised tomography; USG- Ultrasonography; C/S- cut surface; O/E- on examination

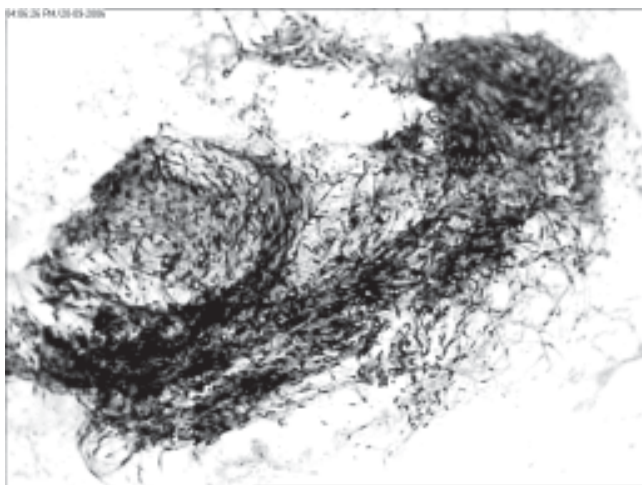


Fig. 1 : Smear showing whorling and palisading of spindle cells (H&E, x 200).

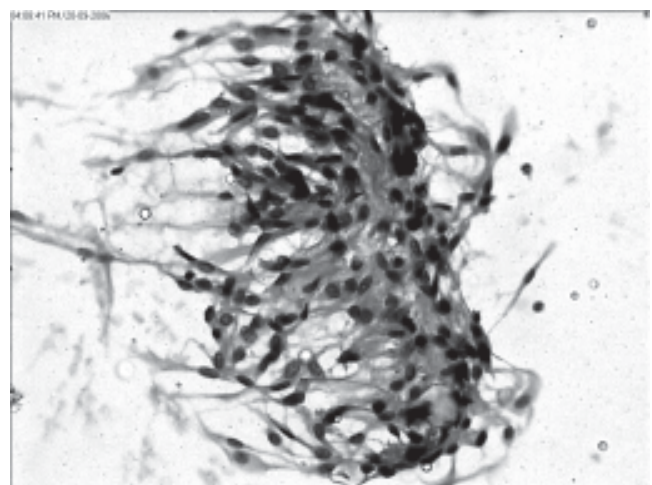


Fig. 2 : Smear showing a group of benign spindle cells with cytoplasm drawn out at both ends (H&E, x 400).

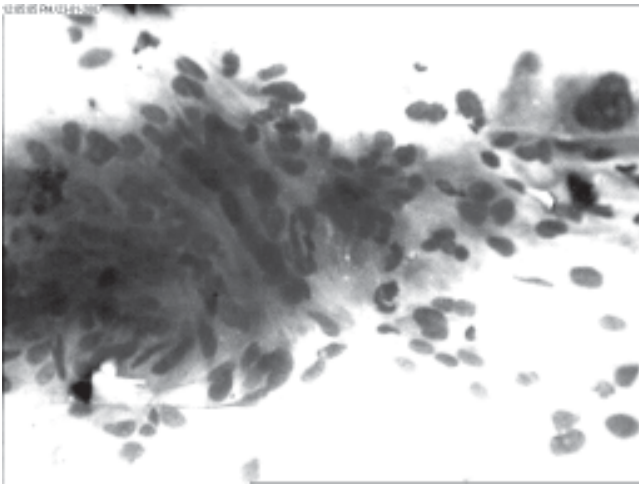


Fig. 3 : Smear showing plump cells in a myxoid background. Large, pleomorphic cells seen (right). (MGG, x 400).

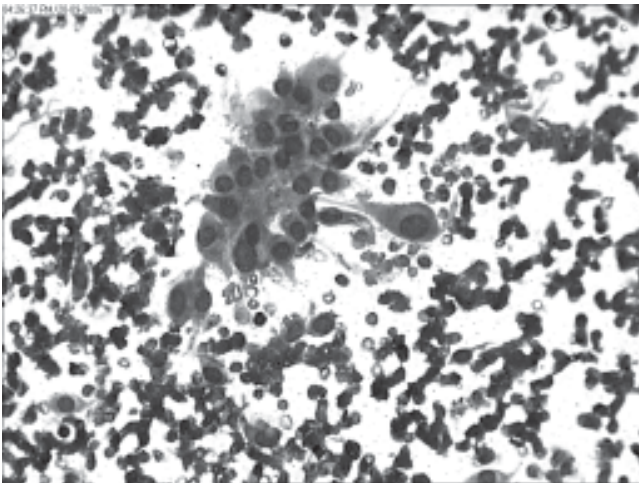


Fig. 4 : Smear showing plump cells with round to oval nuclei displaying pleomorphism and binucleation (MGG, x 400).

occasional inconspicuous nucleoli (Fig. 4). Nuclear pleomorphism and binucleation was also seen (Fig. 4). The diagnosis in this case was GIST (borderline/ malignant).

Gross findings: Resected specimens from all three cases were examined. Two tumours were involving retroperitoneum or peritoneum and adjacent mesentery and were received along with attached bowel loop. One tumour was received with resected portion of stomach and omentum. All tumours were fleshy and solid. Two showed areas of necrosis and haemorrhage.

Histologic findings: Two cases of benign and one case of malignant GIST were diagnosed. Sections from benign GIST showed interlacing fascicles of benign spindle cells with eosinophilic, fibrillary cytoplasm and cigar shaped nuclei. There was no nuclear pleomorphism or mitoses. Few areas of haemorrhage were seen and overlying intestinal mucosa was normal. Sections from malignant GIST showed spindle cells arranged in interlacing bundles and sheets along with solid sheets of polygonal cells (Fig. 5). The cells had moderate to abundant fibrillary eosinophilic cytoplasm. Oval to elongated nuclei with nuclear pleomorphism, multinucleation and 5-7 mitoses/-50 hpf were noted. There were foci of haemorrhage necrosis and inflammatory cells (Fig.6).

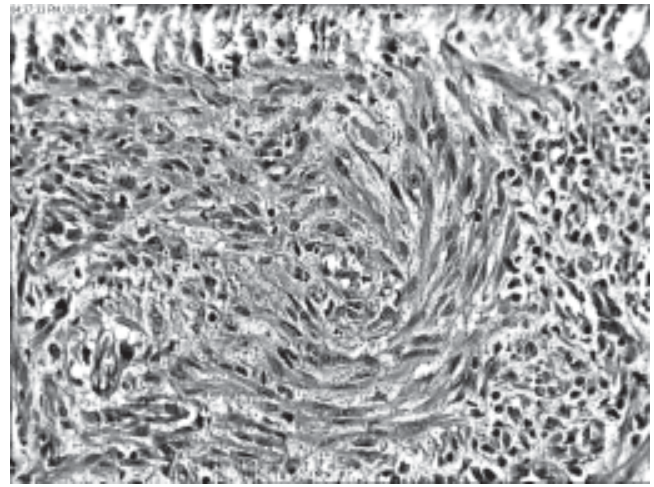


Fig. 5 : Histology section showing whorling. Cells show pleomorphic nuclei, prominent nucleoli and abnormal mitoses (H&E, x 400).

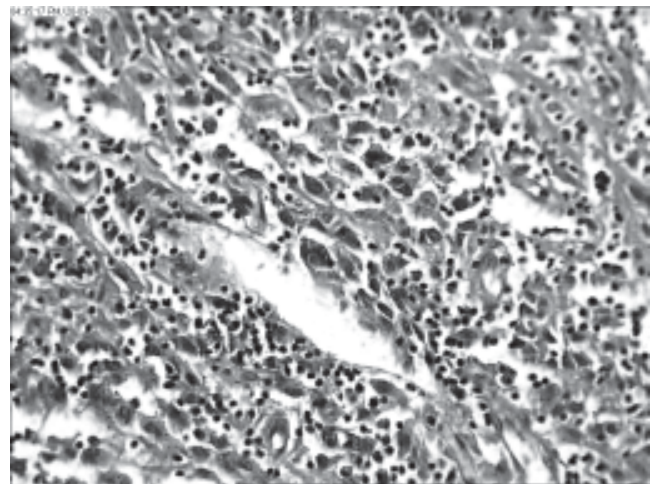


Fig. 6 : Section showing atypical, pleomorphic nuclei, bizarre cells and lymphocytic infiltration (H&E, x 400).

Discussion

GIST is the most common non-epithelial tumour of GIT that is seen most commonly in the stomach (60-70%) followed by small intestine (20-25%) colon and rectum (5%) and oesophagus (<5%). GISTs are now believed to arise from interstitial cells of Cajal (intestinal pacemaker cells) because they express CD 34 and CD 117 (c-kit) antigens. CD 117 is sensitive (79-86%) and relatively specific for GIST. These are believed to arise from primitive stromal cells capable of differentiating into interstitial, smooth muscle, or neural cells because some of these tumours show positivity for smooth muscle and neural markers.

Clinically, most present with an abdominal mass, pain and malena. USG and CT scan show a mass arising from gastric or intestinal wall, displacing adjacent bowel loops⁸. Invasion of adjacent structures or metastases may be present. Morphologically GIST's

may be spindle or epithelioid type.⁴ Spindle cell GISTs are more common. Smears are generally cellular and show a combination of densely cellular, cohesive fragments and dispersed single cells in a clear or slightly haemorrhagic background.^{4,6,8,9} The cohesive cell groups show a branching arrangement with irregular outlines. A fascicular arrangement and nuclear palisading (often more evident on alcohol fixed smears) was seen in two of our cases.^{1,4,6,9} Fibrillary, myxoid material was also seen in one of our cases.^{1,4,6} Individual cells are oval or spindle with an ill-defined wispy cytoplasm which is drawn into processes, and may show perinuclear vacuoles.^{1,4,6-9} Nuclei are oval or elongated, blunt ended with a finely dispersed chromatin and absent or indistinct nucleoli.^{1,6,7,9} Stripped nuclei were seen in all our cases.^{4,6,7,9}

One of our cases showed more obvious pleomorphism, plump nuclei and coarse chromatin and was diagnosed as borderline/malignant GIST. Malignant GIST's show loosely cohesive groups and many dispersed cells with coarse nuclear chromatin and nucleoli.^{4,5,8} Mild nuclear pleomorphism may be observed but significant nuclear pleomorphism and abnormal mitoses are not seen in smears even when they are present in resected tissue.^{1,4,6,9} Metastatic spindle cell GIST's have to be distinguished from leiomyosarcoma, fibrosarcoma, malignant fibrous histiocytoma and other sarcomas, and in the liver from sarcomatoid hepatocellular carcinoma.⁵ Epithelioid GIST's are less common than spindle cell GIST's but pose a greater diagnostic challenge. These show loosely cohesive cell groups and many single round or polygonal cells with moderate to abundant, well-defined cytoplasm round hyperchromatic nuclei with coarse chromatin and nucleoli.^{2,4} Nuclear pleomorphism, binucleation, multinucleation and intranuclear inclusions are common.^{2,4} Epithelioid GIST's have to be distinguished from carcinoma, neuroendocrine tumour, melanoma and hepatocellular carcinoma.

CD 34 and CD 117 positivity has been demonstrated in cell blocks as well as in histology sections.^{1,3,4,7,9} Tumours may show positive staining with either or both, but this has no correlation with either the type or grade of GIST.⁴ CD 117 shows strong and diffuse positivity and is more sensitive and specific than CD 34.^{2,4,5}

Grossly, GIST's are submucosal, usually well circumscribed, may project into the lumen, or may grow outwards with a dumbbell shaped configuration.⁸ They are soft to firm, and show a pale pink, fleshy

or whorled cut surface.^{1,6,8,9} Areas of necrosis and haemorrhage are common and were seen in one of our cases which was diagnosed as malignant GIST. Thorough sampling of solid as well as necrotic, haemorrhagic areas should be done. On histology, GIST's show continuity with muscularis propria with an intact or ulcerated mucosa.^{6,8} One of our cases showed ulceration of the mucosa. Tumours are very cellular with a whorled or palisaded arrangement of spindle cells with fibrillary, eosinophilic cytoplasm.^{1,4,6,8} Nuclei are oval or cigar shaped and display very little pleomorphism or atypia except in malignant tumours.^{4,6} Some tumours show epithelioid cells in sheets with round to polygonal cells having moderate to abundant, eosinophilic or clear cytoplasm with well-defined borders and round to oval, central or eccentric nuclei with vesicular chromatin and a prominent central nucleoli.^{2,4,8} Multinucleation and nuclear pleomorphism are often seen.⁸ The spindle and epithelioid patterns can be admixed and often blend together.²

GIST's have been divided into 4 subtypes on the basis of their differentiation (i) Tumours showing smooth muscle differentiation (ii) Tumours showing neural differentiation (iii) Tumours showing dual differentiation (iv) Tumours lacking differentiation towards either cell type. GIST's are classified into benign, borderline and malignant on the basis of tumour size, mitotic activity and clinical outcome. About 10% GIST's exhibit malignant behavior.⁴ Prognostic factors include age, location (oesophageal and gastric GIST's having a better prognosis than intestinal GIST's), staging, tumour size, mitotic activity. Size and mitoses are most useful predictors. Mutation of c kit gene is a strong prognostic predictor of malignancy. Metastases occur most commonly to liver and peritoneum.²

Many authors believe that a cytologic diagnosis of GIST should not be made without ICC.^{5,7} We believe that this diagnosis can be made with confidence on morphology alone especially in centers like ours where ICC facilities are not available and where the patient's future management depends on the cytologic diagnosis. Cytology is basically useful in classifying the tumour as epithelial vs stromal and spindle vs epithelioid types of GIST.^{1,4} Most cytology smears show a relatively benign picture without obvious pleomorphism, anaplasia or mitoses even when these are seen on histology. Since mitoses form an important criterion for the diagnosis of malignancy, assessment of malignancy should not be attempted on smears

and is best left to histological examination or the final outcome of the patient.^{1,4-6,9} Treatment includes wide surgical resection and administration of tyrosine kinase inhibitors which have proved to be very effective. Because of specific therapy, accurate preoperative diagnosis is very useful and can help plan surgery in resectable lesions or alternative therapy in unresectable or metastatic lesions.^{2, 9}

References

1. Boggino HE, Fernandez MP, Logrono R.F Cytomorphology of gastrointestinal stromal tumour: diagnostic role of aspiration cytology, core biopsy, and immunochemistry. *Diagn Cytopathol* 2000;23:156-60.
2. Dong Q, McKee G, Pitman M, Geisinger K, Tambouret R. Epithelioid variant of gastrointestinal stromal tumour: diagnosis by fine-needle aspiration. *Diagn Cytopathol* 2003; 29: 55-60.
3. Gu M, Ghafari S, Nguyen PT, Lin F. Cytologic diagnosis of gastrointestinal stromal tumours of the stomach by endoscopic ultrasound-guided fine-needle aspiration biopsy : cytomorphologic and immunohistochemical study of 12 cases. *Diagn Cytopathol* 2001; 25: 343-50.
4. Li SQ, O'Leary TJ, Buchner SB, et al. Fine needle aspiration of gastrointestinal stromal tumours. *Acta Cytol* 2001; 45: 9-17.
5. Cheuk W, Lee KC, Chan JK. c-kit immunocytochemical staining in the cytologic diagnosis of metastatic gastrointestinal stromal tumour. A report of two cases. *Acta Cytol* 2000;44: 679-85.
6. Dodd LG, Nelson RC, Mooney EE, Gottfried M. Fine-needle aspiration of gastrointestinal stromal tumours. *Am J Clin Pathol* 1998; 109: 439-43.
7. Kimura M, Satou T, Hashimoto S, Tabaru Y. Can GIST be diagnosed reliably by cytology? *Acta Cytol* 2002; 46: 1170-1.
8. Isimbaldi G, Santangelo M, Cenacchi G, et al. Gastrointestinal autonomic nerve tumour (plexosarcoma): report of a case with fine needle aspiration biopsy and histologic, immunocytochemical and ultrastructural study. *Acta Cytol* 1998; 42:1189-94.
9. Kwon MS, Koh JS, Lee SS, Chung JH, Ahn GH. Fine needle aspiration cytology (FNAC) of gastrointestinal stromal tumour: an emphasis on diagnostic role of FNAC, cell block, and immunohistochemistry. *J Korean Med Sci* 2002;17: 353-9.