DE NOVO DEDIFFERENTIATED GASTRO-INTESTINAL STROMAL TUMOR (GIST) OF DUODENUM - FIRST CASE REPORTED IN THE WORLD

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. The interstitial cell lineage of Cajal have been accepted to be the cell of origin to these tumors. The tumor cells of major GISTs usually express KIT (CD117) protein or DOG-1 and the majority of them show activating mutations in either the KIT or platelet-derived growth factor receptor alpha (PDGFRA) proto-oncogenes

The tumours occasionally undergo dedifferentiation to exhibit morphological and phenotypic changes. Dedifferentiation is the regression of cells towards a less differentiated state in which the original lineage specific gene expression is no longer evident. Dedifferentiation can occur in two conditions—after prolonged treatment with imatinib, or can occur denovo. To establish such rare finds of de novo differentiation, we report the first known reported case of a de novo dedifferentiated GIST of duodenum in the world.

CASE PRESENTATION

A 64-year-old man presented with reports of epigastric abdominal pain along with a history of rectal bleeding and dark coloured stools for over a month. Physical examination was normal without any significant findings. In view of the above symptoms, he underwent a colonoscopy and upper gastrointestinal endoscopy which revealed an ulcerated lesion in the duodenum and periampullary area. There was no history of gastric outlet obstruction.

INVESTIGATIONS

A positron emission tomography-CT (PET-CT) scan revealed a metabolically active irregular ulcerating soft tissue thickening involving the anterior and medial wall of the D2 segment of duodenum extending into the D3 segment measuring up to 3.2cm in thickness and extending for a length of 7.8cm infiltrating the head of the pancreas (CT scan - figure 1). Also seen was prominent lymph nodes measuring 3.1x2.3 cms (Figure 2)

An endoscopic biopsy was taken and on histopathology, the biopsy revealed malignant spindle cell neoplasm with smooth muscle differentiation.On immunohistochemistry (IHC), the tumour cells stained focally positive for smooth muscle antigen (SMA) and diffusely positive for calponin while being negative for CD117, DOG-1, CD-34, h-caldesmon, ALK-1, S100 and panCK.

TREATMENT

A multidisciplinary approach was adopted and surgical resection of the mass was decided. A complete blood and metastatic workup was followed up after which a collective plan to perform Whipple pancreaticoduodenectomy was made.

Intraoperative exploration revealed a large mass of dimensions 8×7cm involving first and second part of duodenum, with infiltration into the pancreatic head (figure 3). The lesion was also found infiltrating into the
transverse mesocolon, which was simultaneously removed. There was desmoplastic reaction around the tumour without any evidence of peritoneal or liver metastasis. The mass was soft to firm in consistency (figure 4), tan white in colour with areas of myxoid changes and haemorrhage.

Microscopic examination revealed a highly cellular tumour formed of fascicles of ovoid to spindle shaped cells (figures 5 and 6) with areas of pleomorphism and many scattered bizarre tumour giant cells (figure 7). The lesion had appearance of pleomorphic sarcoma. The lesion extended from the submucosa through the
muscularis propria and serosa of the duodenum, with infiltration to the adjacent pancreas. Only 5% of tumour showed typical appearance of GIST (Figure 5 and 6) and was positive for CD117 (Figure 8B). Majority of tumour cells which were composed of bizarre anaplastic tumour cells were

negative for c-kit (figure 8A). Among the other IHC markers, the pleomorphic tumour cells were negative for DOG-1 (figure 8C), S100, CD-34, SOX10, P53, h-caldesmon, ALK-1, desmin and panCK. SMA positivity was noted on IHC in the areas of spindle cells, typical of GIST (figure 8D). On a molecular level, for the two areas of the tumor, activating mutations for the KIT gene (exons 9, 11, 13, 17) were negative along with no activating mutations detected for the PDGFRA gene in either component. No prior pre-surgical therapy was given, which strongly suggest that the dedifferentiation components were de novo in origin. A final diagnosis of denovo dedifferentiated GIST was made in this case based on focal GIST like areas and CD117 positivity.

OUTCOMES AND FOLLOW-UP

Postoperative course was uneventful and the patient was discharged after 7days.

DISCUSSION

GISTs may exhibit morphological and phenotypic changes and differentiate into an unusual phenotype through the process of dedifferentiation. Dedifferentiation is a cellular process reverting cells to a less differentiated stage. Dedifferentiation plays an important role in cell immortality causing resistance to therapy in recurring and metastatic tumours. Until recently, dedifferentiated anaplastic variants of GISTs were reported only in patients who had received long-term treatment with the tyrosine kinase inhibitor imatinib mesylate. More recently, however, cases of de novo dedifferentiated GISTs, irrespective of treatment with a therapeutic agent, were reported. These tumours can be diagnostically challenging due to their obvious anaplastic appearance and lack of CD117 expression.

Histologically, the area of pleomorphic sarcoma usually demonstrated a sharp transition from the classical GIST component corresponding to the greyish–white and pinkish areas of the gross specimen. The dedifferentiated component was highly cellular with marked pleomorphism and had frequent mitoses. Also, necrotic areas were frequently seen.

De novo dedifferentiated GISTs have only been reported in a handful of cases. It has been shown that dedifferentiation can occur de novo through KIT-independent mechanisms with loss of KIT expression and altered morphology. Remarkably our case did not demonstrate c kit or PDGFR mutation. It is important to increase the awareness of such findings among various other differentials as they pose a diagnostic challenge and have an unclear response to targeted molecular therapy as compared with their c-kit positive counterparts.
De novo dedifferentiated GIST in the duodenum with wild type c kit has never been reported in the world until now. Ours is the first case reported.

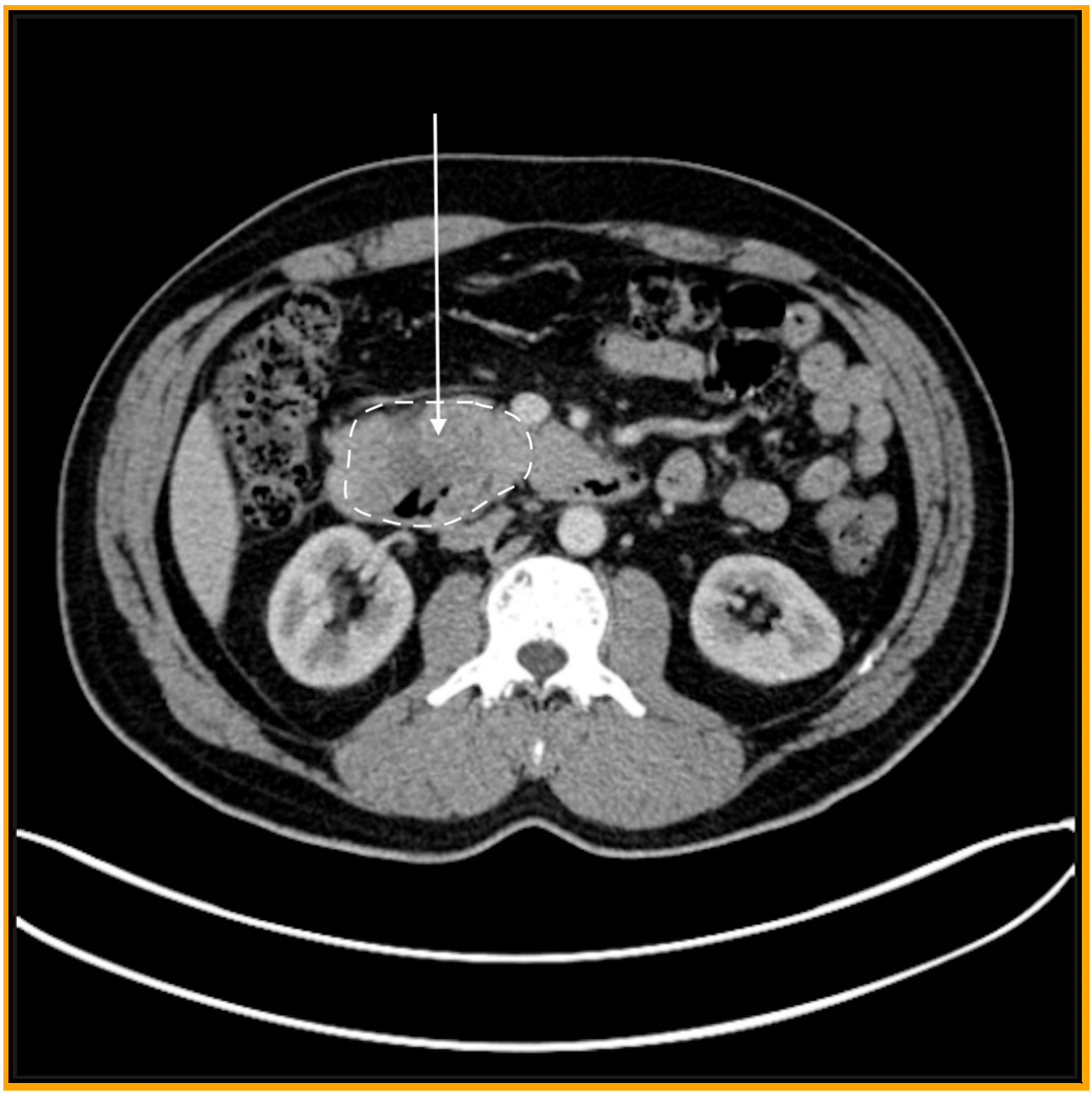

Figure 1 CT scan. Dotted lining showing the margins of the tumour.

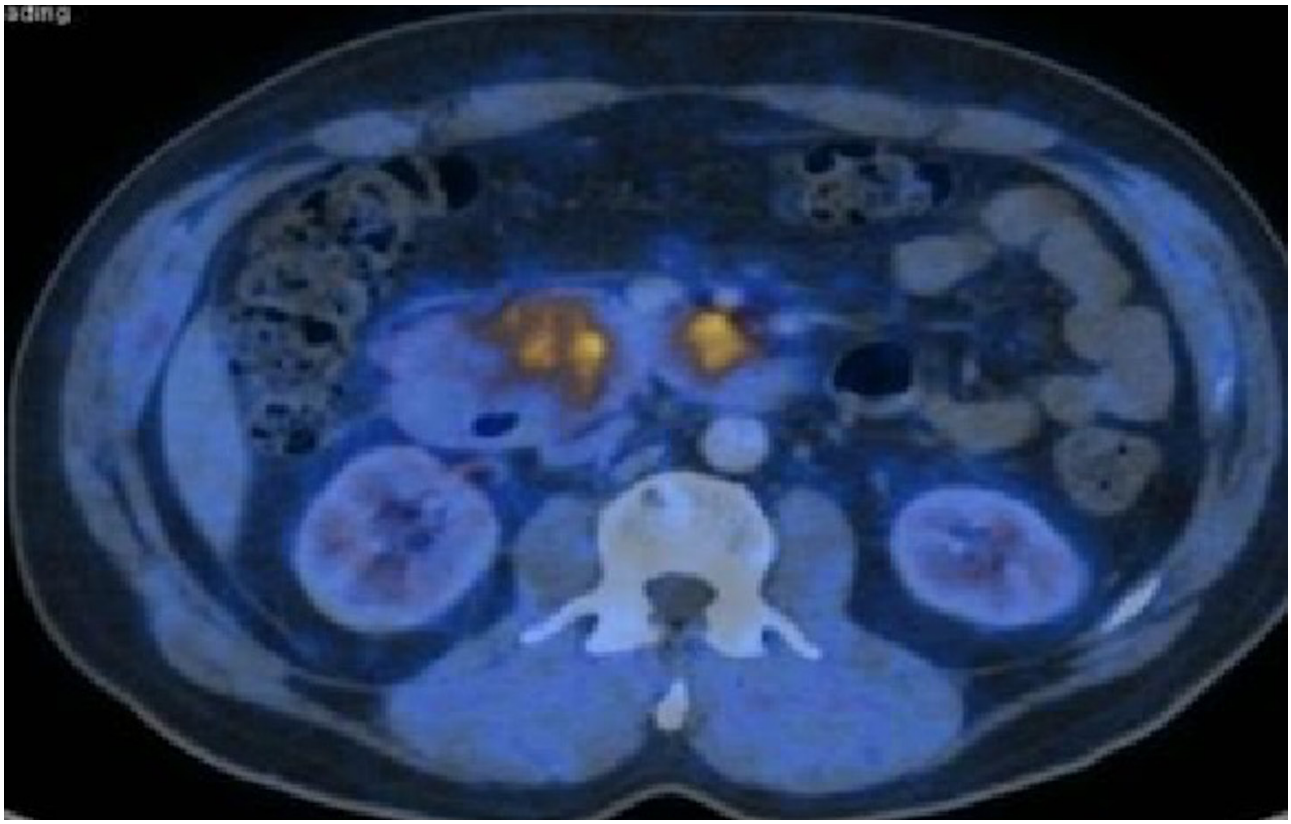

Figure 2 Positron emission tomography scan. Corresponding area of the CT scan shows the activity of the tumour.

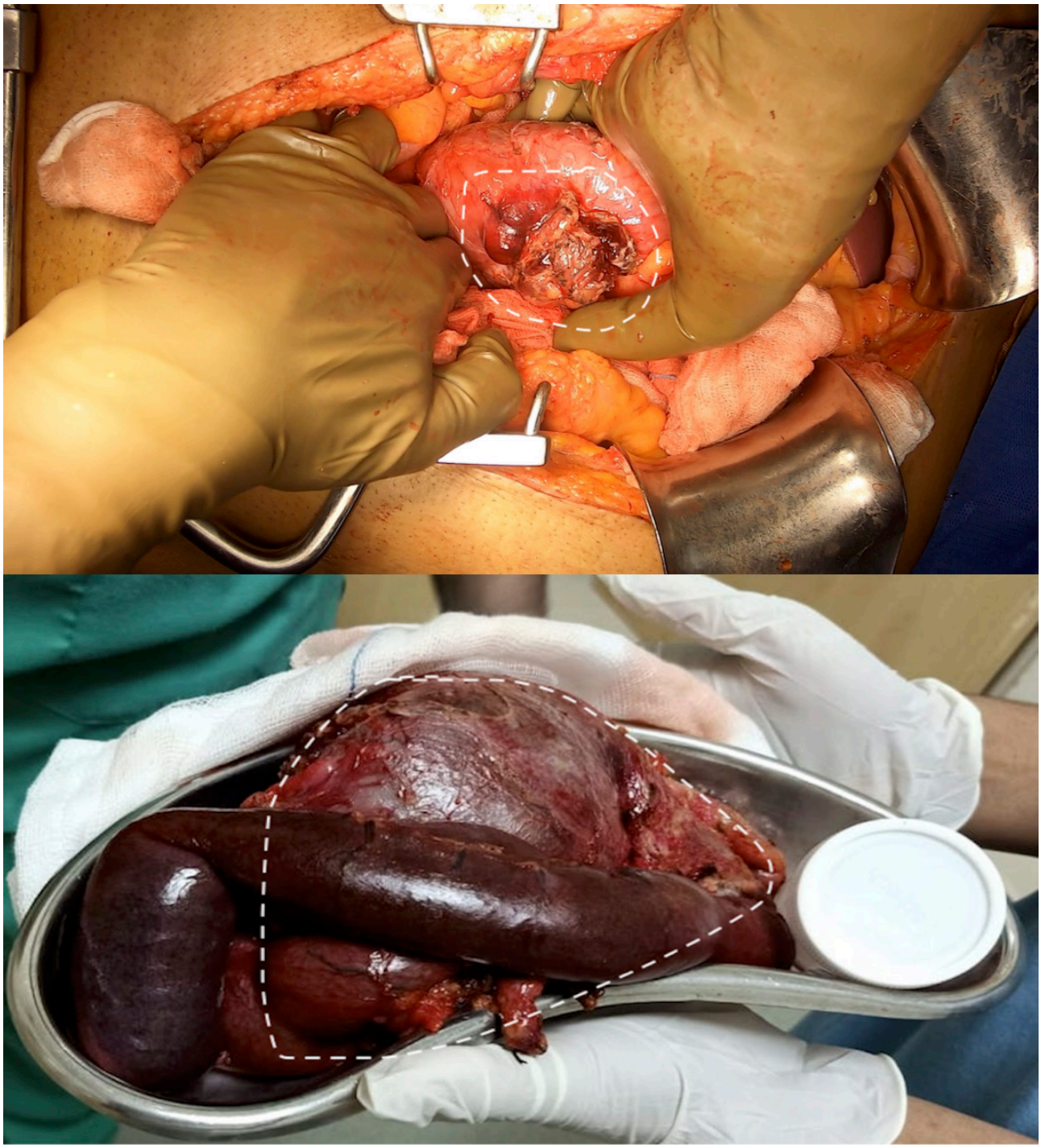

Figure 3 Intraoperative tumour mass (above) with resected specimen after Whipple's procedure(below). Solid, lobulated appearance of the mass along the duodenum infiltrating the head of the pancreas.

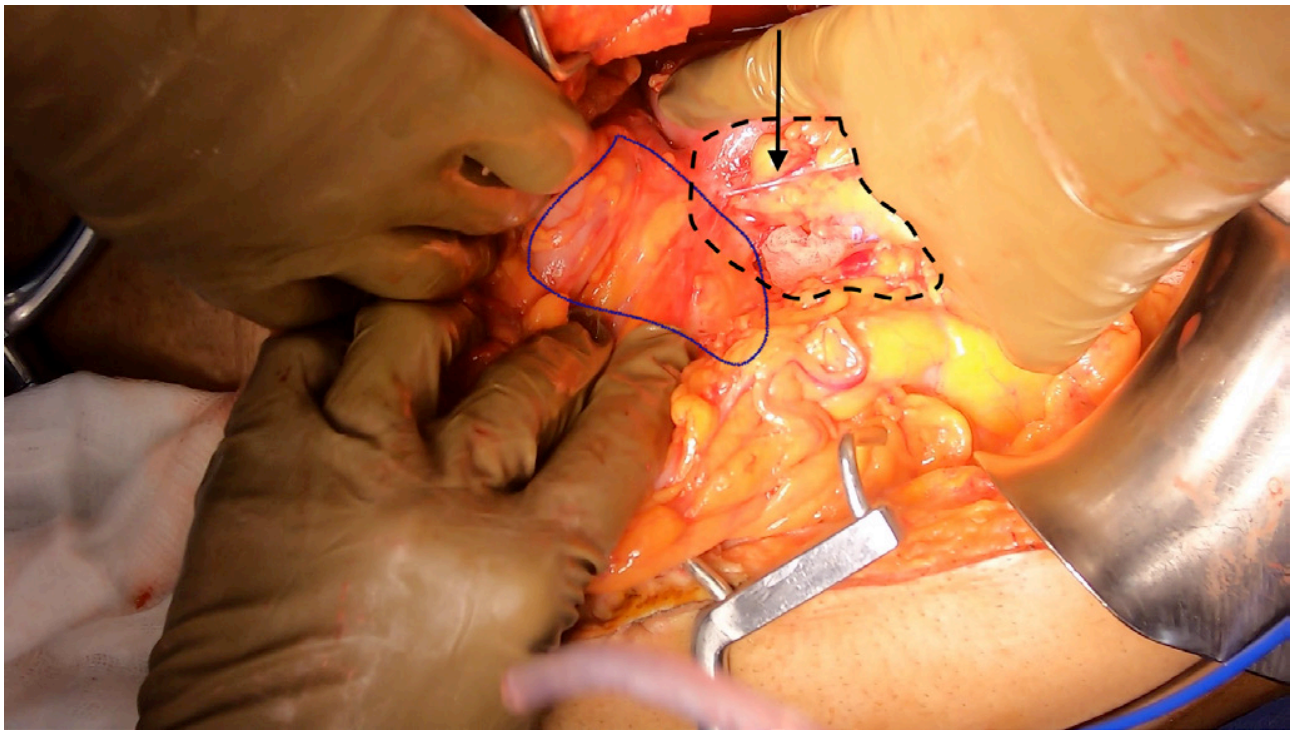

Figure 4 (Dotted region with arrow) Area of tumour infiltration and invading into the head of the pancreas. (Solid line encircled region) Area of desmoplastic response.

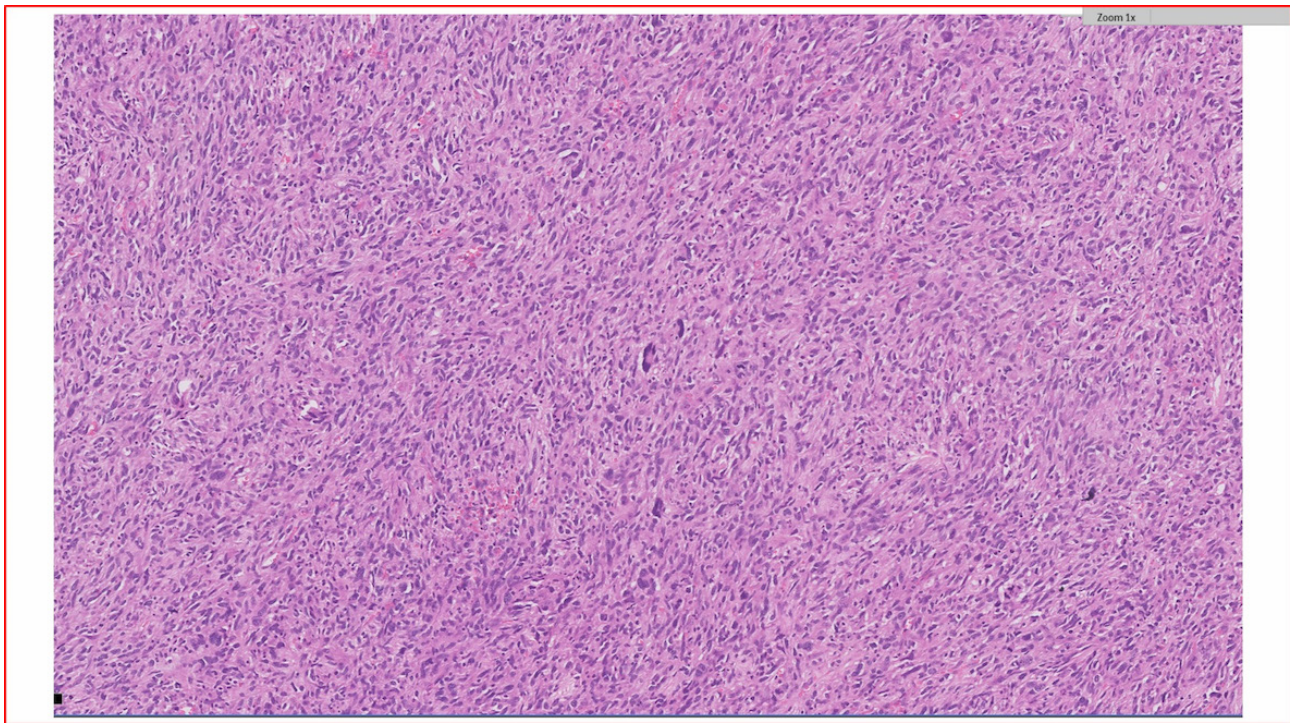

Figure 5 Fascicles of spindle shaped cells with scattered giant cells, H&E (10×).

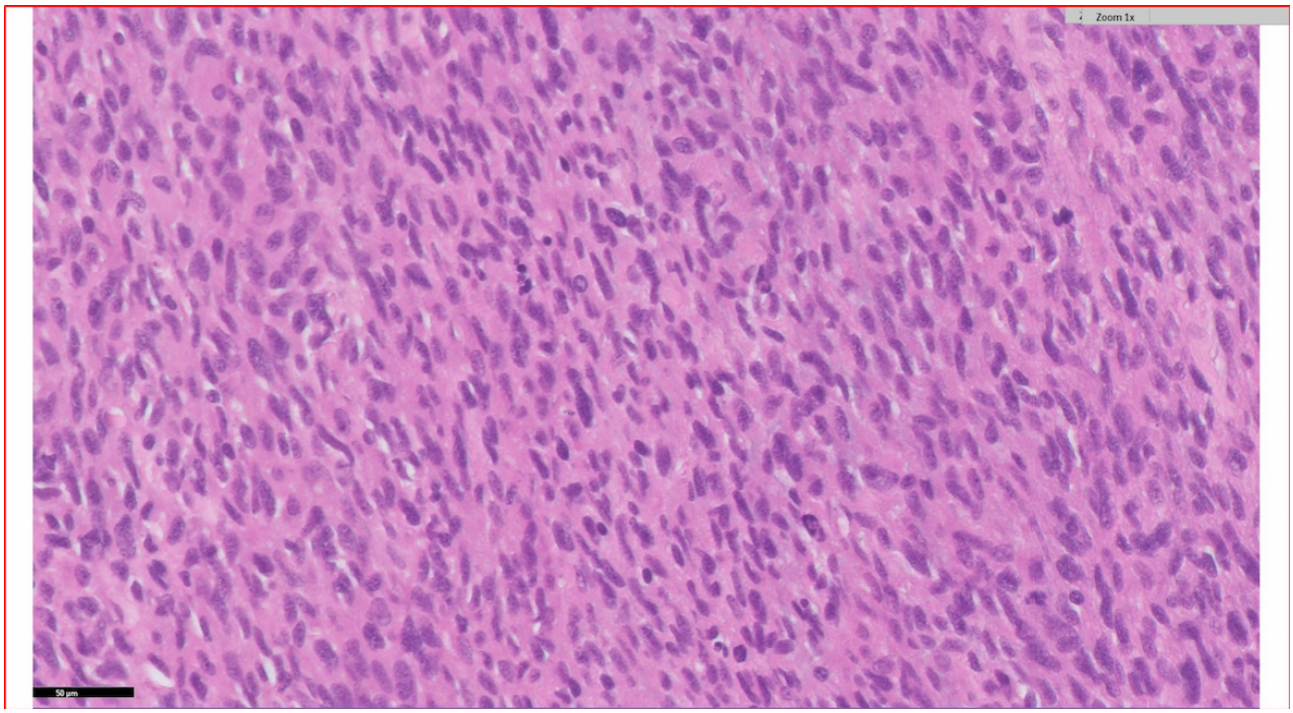

Figure 6 Typical spindle cells in haphazard fascicles. H&E (20x)

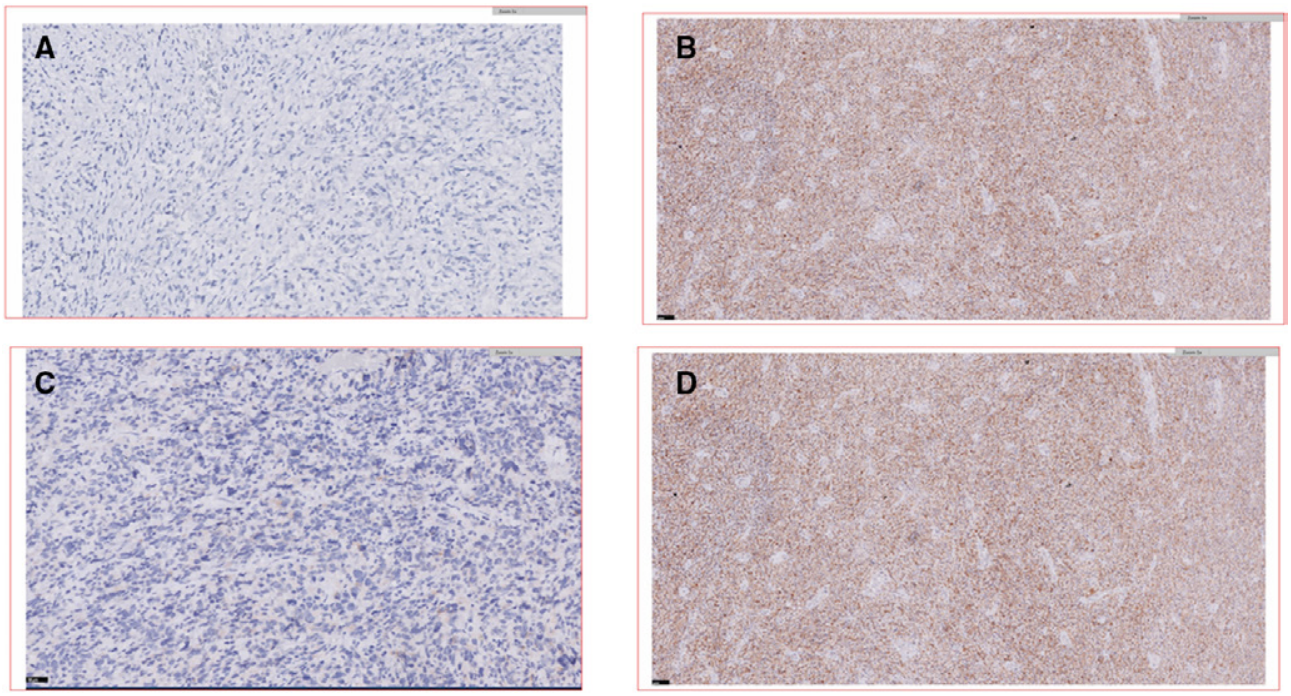

Figure 8 Immunohistochemistry study. Bizarre areas negative for c-kit and DOG-1, while spindle cell areas positive for CD117 and smooth muscle antigen (top left (A), top right (B), bottom left (C), bottom right (D)).