Gastrointestinal stromal tumors (GISTs) are rare tumors of the gastrointestinal tract accounting for less than 1% of all gut tumors. GISTs occurring in the rectum are extremely rare and these usually present at an advanced stage compared with other sites.

We report a case of a middle-aged female who presented with features of anemia and subacute obstruction due to a large rectal tumor and underwent abdominoperineal resection. The histopathological examination confirmed the diagnosis of high-grade malignant GIST with multiple lymph nodal metastasis. She was started on adjuvant imatinib therapy and is on follow-up without any evidence of recurrence.

The authors conclude that GIST must be included in the differential diagnosis of a rectal tumor. Diagnosis is established by biopsy and immunohistochemistry studies. Surgical resection with histological negative margins is the standard curative treatment. Adjuvant targeted therapy can reduce long-term recurrence in high-risk cases.
polypoidal wall thickening showing contrast enhancement, extending from just above the anal verge up to the rectosigmoid junction, with surrounding mesorectal fat stranding and multiple enlarged perirectal nodes (►Fig. 1).

Magnetic resonance imaging (MRI) of the pelvis was done in our institution. It showed a diffuse polypoidal endoluminal lesion extending from 3.5 cm above anal verge up to the rectosigmoid junction measuring approximately 14-cm long with infiltration into mesorectal fat, thickening of mesorectal fascia, anal sphincter involvement and multiple enlarged perirectal and bilateral internal iliac nodes (►Fig. 2).

Proctoscopy-guided biopsy of the lesion was reported as amelanotic type of malignant melanoma. Sigmoidoscopy could not be performed due to large size of the growth. CT scans of the abdomen and chest did not reveal any distant metastasis.

The patient was optimized with blood transfusion and intravenous fluids with electrolyte supplementation. Since she had persistent bleeding from the tumor and had features suggestive of intermittent subacute intestinal obstruction, she was taken up for surgery as per the opinion of the institutional multidisciplinary tumor board and underwent laparoscopic abdominoperineal excision (APE) of rectum (►Fig. 3).

The histopathological examination (HPE) showed a 11-cm pedunculated proliferating mass formed by of a neoplasm composed of spindle shaped cells arranged in fascicles and bundles, and involving up to serosa of the bowel wall and anal sphincters, with mitotic count of 25/50 high power fields (HPF), and all 14 lymph nodes harvested showed metastatic deposits. Diagnosis of GIST was confirmed by immunohistochemistry (IHC) which was positive for CD 117 and CD 34, and negative for CK (cytokeratin), S-100, HMB 45 (human melanoma black 45), and α-SMA (smooth muscle actin; ►Fig. 4).
tumor size, morphology, depth of endoscopic ultrasound (EUS) is helpful in evaluation of submucosal mass. Multimodal imaging with CT, MRI, and endoscopy, rectal GIST can be seen as an intraluminal or a commonly have an exophytic growth pattern. On sigmoid-

These tumors present with bleeding per rectum, lower abdominal pain, tenesmus, constipation, urinary symptoms, and may be occasionally asymptomatic. Even if it had been reported as GIST, upfront resection could be justified due to its large size causing luminal obstruction and presence of persistent bleeding from the tumor. There are similar case reports of large anorectal GISTs managed by abdominoperineal excision.

Gastrointestinal stromal tumors (GISTs) originate from the interstitial cells of Cajal and stain positive for CD117, a product of c-kit protooncogene involved in the regulation of cell proliferation. Majority of GISTs develop due activating mutations in the c-kit or the platelet-derived growth factor receptor A (PDGFRA).

About 5% of all GISTs occur in the rectum and they account for 0.1% of all tumors originating in the rectum. Only three cases of rectal GIST were treated at our institution over a 3-year period from 2017 to 2020, including our patient. The choice of surgical procedure (local excision, anterior resection, and abdominoperineal excision of rectum) depends on tumor size and location. Whenever feasible, sphincter-preservation resection is recommended. If abdominoperineal excision of rectum is needed to achieve margin negative resection, then preoperative chemotherapy is recommended. The anus-preservation rate following chemotherapy has been reported to range from 33 to 94.9%. Several case reports have demonstrated that use of preoperative (neoadjuvant) imatinib enables sphincter-sparing resection and improves survival for rectal GISTs. Since preoperative biopsy was reported as melanoma in our case, upfront resection was performed. Even if it had been reported as GIST, upfront resection could be justified due to its large size causing luminal obstruction and presence of persistent bleeding from the tumor. There are similar case reports of large anorectal GISTs managed by abdominoperineal excision.

A final diagnosis of malignant GIST of the rectum stage IV (T4 N1 M0), as per the American Joint Committee on Cancer (AJCC) staging system, was made. Postoperative period was uneventful. She recovered well and was discharged on postoperative day 11. She was started on imatinib adjuvant therapy (400-mg daily). She is on regular follow-up for the past 30 months, with contrast-enhanced CT of abdomen and pelvis done once every 6 months, without any evidence of recurrence.

Discussion

Gastrointestinal stromal tumors (GISTs) constitute 10 to 15% of all GISTs. DOG1 immunostaining is useful in cases that cannot be categorized as GIST based on histology. Most tumors originate within the muscularis propria and are often heterogeneous due to areas of hemorrhage, necrosis, or cystic degeneration. These tumors commonly present with distant metastasis (47%). Positron emission tomography (PET) is useful for detection of metastasis and for assessing response to medical therapy. As per NCCN guidelines, PET is not routinely recommended for staging except for clarification of ambiguous findings on cross-sectional imaging and when neoadjuvant therapy is planned. PET was not done in our case. Instead, staging laparoscopy was performed at the time of definitive surgery to rule out peritoneal metastasis.

Biopsy with immunohistochemical analysis is crucial for accurate diagnosis, for initiating neoadjuvant therapy, and for surgical planning. Histologically, these tumors may exhibit a spindle pattern, an epithelioid pattern, or a mixed subtype. Others tumors that can mimic GIST on histology include leiomyoma, leiomyosarcoma, desmoid, neuroendocrine tumor, fibrous tumors, melanoma, and other sarcomas. Positive expression of CD117 (c-kit) is the major diagnostic criteria with high sensitivity (95%). Rectal GISTs also show high incidence of CD34 positivity (90%). (Detected on GIST-1 (DOG1) is a recently identified marker with sensitivity similar to CD117 in the diagnosis of these tumors, including wild-type GISTs which have no detectable c-kit or PDGFRA mutations and constitute 10 to 15% of all GISTs. DOG1 immunostaining is useful in cases that cannot be categorized as GIST based on CD117 immunostaining and mutation testing for KIT and PDGFRA. In our case, preoperative biopsy was reported as amelanotic melanoma but IHC study was not done.

Complete surgical resection with histologically negative margins (R0 resection) is the standard curative procedure for localized tumors and is essential to prevent recurrence. Care must be taken to avoid intraoperative tumor rupture. As these tumors do not spread through lymphatics, routine lymph node dissection is unnecessary except if lymph node involvement is suspected during surgery. The incidence of lymph-node metastasis in GISTs overall has been reported to be around 1%. The prognostic significance of nodal metastasis has not been clearly established. Our patient had extensive pelvic lymph node metastasis which has been reported rarely in the literature.

The choice of surgical procedure (local excision, anterior resection, and abdominoperineal excision of rectum) depends on tumor size and location. Whenever feasible, sphincter-preservation resection is recommended. If abdominoperineal excision of rectum is used to achieve margin negative resection, then preoperative chemotherapy is recommended. The anus-preservation rate following chemotherapy has been reported to range from 33 to 94.9%. Several case reports have demonstrated that use of preoperative (neoadjuvant) imatinib enables sphincter-sparing resection and improves survival for rectal GISTs. Since preoperative biopsy was reported as melanoma in our case, upfront resection was performed. Even if it had been reported as GIST, upfront resection could be justified due to its large size causing luminal obstruction and presence of persistent bleeding from the tumor. There are similar case reports of large anorectal GISTs managed by abdominoperineal excision.

The Surgery Journal Vol. 8 No. 1/2022 © 2022. The Author(s).
Laparoscopic resection has been successfully performed for rectal GISTs. Laparoscopic APE had to be done in our case due to extensive sphincter involvement as per imaging and ongoing bleeding from tumor. Transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS) have also been performed for rectal GISTs with good success.

About 40 to 50% of GISTs will recur or develop metastasis even after a curative resection. Criteria, such as the Fletcher criteria, Armed Forces Institute of Pathology (AFIP) criteria, and Joensuu criteria, have been developed to predict the risk of disease recurrence. These are based on factors such as tumor size, mitotic count, tumor location, and presence of tumor rupture. Those who are in high-risk category benefit from adjuvant therapy. Rectal GISTs tend to have aggressive biological behavior and tumors with high mitotic activity can recur and metastasize despite a small size of <2 cm. Predicted metastasis rate in our case as per AFIP criteria was 71 to 90% and belonged to high-risk category.

Adjuvant therapies using small-molecule tyrosine kinase inhibitors, imatinib mesylate and sunitinib, have demonstrated good results in improving survival. These drugs act by selectively blocking c-kit function and thereby halting proliferation. Those with c-kit mutation at exon-11, which has been reported commonly in rectal GISTs, respond better to treatment than those with mutation at exon-9. Thus, c-kit mutation genotype analysis is essential before starting therapy whenever feasible. In a landmark trial by DeMatteo et al, the use of imatinib in the adjuvant setting was shown to prolong survival in high-risk tumors. Criteria, such as the Fletcher criteria, Armed Forces Institute of Pathology (AFIP) criteria, have been developed to predict the risk of disease recurrence. These are based on factors such as tumor size, mitotic count, tumor location, and presence of tumor rupture. Those who are in high-risk category benefit from adjuvant therapy. Rectal GISTs tend to have aggressive biological behavior and tumors with high mitotic activity can recur and metastasize despite a small size of <2 cm. Predicted metastasis rate in our case as per AFIP criteria was 71 to 90% and belonged to high-risk category.

There is no definite consensus on the optimal duration of adjuvant therapy but is generally recommended for a period of 3 years.

Tumor size, mitotic index, R0 resection, and c-kit positivity are important prognostic factors. Benign GISTs have no evidence of local invasion and have low mitotic activity, and thus have favorable prognosis with local excision alone. Malignant GISTs are locally invasive and/or metastatic at presentation, or recur after resection. These tumors are usually large (≥5 cm) and have a high mitotic count (>5/50 HPF). Patients with malignant GISTs have an overall 5-year survival rate of approximately 45%. The recurrence rate has been shown to be as high as 40% even after early resection. Majority of recurrences occur either locally or in the liver. Hence, long-term follow-up with 3 to 6 monthly imaging for 3 to 5 years and then annually is generally recommended.

Conclusion

Gastrointestinal stromal tumors are rare malignancies involving the rectum. Diagnosis is established by biopsy and immunohistochemistry. Lymph node metastasis is very rare. Complete surgical resection with negative margins is the treatment of choice. The appropriate surgical technique should be selected based on location, size, and resectability of tumor and the available surgical expertise. Adjuvant imatinib therapy prolongs survival in high-risk tumors.

This case is reported for its rarity and presentation with lymph nodal metastasis.

Conflict of Interest
None declared.

References
1. Grassi N, Cipolla C, Torcivia A, et al. Gastrointestinal stromal tumour of the rectum: report of a case and review of literature. World J Gastroenterol 2008;14(08):1302–1304
2. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231(01):51–58
3. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 2005;100(01):162–168
4. Kalkmann J, Zeile M, Antoch G, et al; German GIST Imaging Working Group. Consensus report on the radiological management of patients with gastrointestinal stromal tumours (GIST): recommendations of the German GIST Imaging Working Group. Cancer Imaging 2012;12:126–135
5. Choi H, Charnsangavej C, de Castro Faria S, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. AJR Am J Roentgenol 2004;183(06):1619–1628
6. Casali PG, Blay JY, Bertuzzi A, et al; ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3):iii21–iii26
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): gastrointestinal stromal tumors (GISTs). Version 1.2021, Accessed January 10, 2022 at: https://www.nccn.org/guidelines/guidelines-process/ transparency-process-and-recommendations/GetFileFromFileManagerId=11379
8. Wong HH, Chengal R, Hardwick R, et al. Mimics of gastrointestinal stromal tumours (GISTs): implications for diagnosis and management—the Cambridge GIST study group (CGG) experience. J Clin Oncol 2013;31(15 Suppl):e21503–e21503
9. Fletcher CDM, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumours: a consensus approach. Hum Pathol 2002;33(05):459–465
10. Miettinen M, Sobin LH, Sarlomo-Rikala M. Immunohistochemical spectrum of GISTS at different sites and their differential diagnosis with a reference to CD117 (KIT). Mod Pathol 2000;13(10):1137–1142
11. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. Am J Surg Pathol 2009;33(09):1401–1408
12. Shafizad A, Mohammadianpanah M, Nasrolahi H, Mokhtari M, Mousavi SA. Lymph node metastasis in gastrointestinal stromal tumor (GIST): to report a case. Iran J Cancer Prev 2014;7(03):171–174
13. Chen CW, Wu CC, Hsiao CW, et al. Surgical management and clinical outcome of gastrointestinal stromal tumor of the colon and rectum. Z Gastroenterol 2008;46(08):760–765
14. Kameyama H, Kanda T, Tajima Y, et al. Management of rectal gastrointestinal stromal tumor. Transl Gastroenterol Hepatol 2018;3:8
15. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8(Suppl 2):S1–S41, quiz S42–S44
Singhal S, Singhal A, Tugnait R, et al. Anorectal gastrointestinal stromal tumor: a case report and literature review. Case Rep Gastrointest Med 2013;2013:934875

Joshi A. Anorectal gastrointestinal stromal tumour: a case treated with radical surgery. J Nepal Health Res Coun 2018;16(01):99–101

Rivera AKU, Jabies AG, Passiuri IC, et al. Gastrointestinal stromal tumour of the rectum and intestinal obstruction: case report. Ecancermedicalscience 2020;14:1139

Somu K, Dashore AR, Shah AR, Anandh R. Laparoscopic excision of large lower rectal gastrointestinal stromal tumour (GIST): a case report. J Minim Access Surg 2016;12(03):283–285

Nepal P, Mori S, Kita Y, et al. Management of a case of high-risk gastrointestinal stromal tumor in rectum by transanal minimal invasive surgery. World J Surg Oncol 2018;16(01):165

Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23(02):70–83

Joensuu H, Eriksson M, Hall KS, et al. Risk factors for gastrointestinal stromal tumor recurrence in patients treated with adjuvant imatinib. Cancer 2014;120(15):2325–2333

Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21(23):4342–4349

DeMatteo RP, Ballman KV, Antonescu CR, et al; American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team for the Alliance for Clinical Trials in Oncology. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (Alliance) intergroup phase 2 trial. Ann Surg 2013;258(03):422–429

Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307(12):1265–1272

Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant imatinib for high-risk gastrointestinal tumor: analysis of a randomized trial. J Clin Oncol 2016;34(03):244–250

Miettinen M, Lasota J. Gastrointestinal stromal tumors—definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001;438(01):1–12