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Peripheral Primary Neuroectodermal Tumour of the Ileum: A Case Report and Review of the Literature

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Abstract

Background: Ewing's Sarcoma (ES)/peripheral Primitive Neuroectodermal Tumor (pPNET) is a rare aggressive malignant small round cell tumour. Most of them arise in bony sites, and they represent the second commonest primary osseous malignancy in adolescence and young adults. The localization of the small bowel is very rare, to our knowledge only 35 cases of ES/pPNET of the small bowel have been reported in the literature. **Case Presentation:** We report a case of pPNET of the ileum in a 26-year-old female, presented abdominal pain with a transit disorder. The clinical examination was unremarkable. The histological and immunohistochemical study confirmed the diagnosis of peripheral primary neuroectodermal tumours. The patient was treated by tumor resection followed by adjuvant chemotherapy. The evolution was good, without recurrence with a follow-up of 12 months. **Conclusion:** PNET of the ileum is very rare. We report this case to enrich the database of this rare clinical entity and to improve the management of patients with PNET of the ileum.

Keywords

Ewing's Sarcoma, Primitive Neuroectodermal Tumor, Small Bowel Sarcoma, Extraosseous Sarcoma

1. Introduction

Peripheral primitive neuroectodermal tumors are small round cell neoplasms with neuroectodermal differentiation that develop outside the central and sympathetic nervous systems. These very rare tumors have the similar biochemical and oncogenic expression to several other tumors, such as Askin's tumor or

Ewing's sarcoma, making them members of the Ewing's sarcomatous tumor family [1].

Although ES/PNET are primarily seen in bone and soft tissue in children and young adults, primitive visceral sites have also been reported such as the kidney, uterus, ovary, gallbladder, parotid gland, pancreas, lung, adrenal gland, esophagus and testicle [2] [3] [4] [5] [6]. Although it has been reported previously in this location [7] [8], ES/PNET is extremely rare in the small bowel.

Patients with ES/PNET tumors should be managed by multidisciplinary teams in or der to benefit from an optimal therapeutic strategy.

The present study reports a case of pPNET in the ileum in a 26-year-old woman, and describes the presenting symptoms, imaging findings, anatomopathological features of these tumors.

2. Case Report

A 26-year-old female patient, medical history was unremarkable, presented abdominal pain dating back to 3 months accompanied by alternating diarrhea and constipation evolving in a context of conservation of the general state. The abdominal examination on admission was normal, as was the rest of the physical examination.

Computed Tomography (CT) scanning of the abdomen revealed a 78 × 60 mm mass in the left lower abdominal compartment, the mass had a close contact with the left colon. Gastrointestinal Stromal Tumour (GIST) was suspected (**Figure 1**). Bone scintigrapphy and chest CT scan were unremarkable.

The patient underwent an exploratory laparotomy, and tumor resection was performed along with 40 cm of ileum. The specimen was sent for histopathological evaluation (**Figure 2**).

Macroscopic examination revealed a solid homogenous tumor mass measured 7 × 5 × 4 cm, was found arising from the ileum, nodular greyish-white with foci of necrosis and hemorrhage. Microscopically, the tumor is made up of proliferation of small round and oval tumor cells with high mitosis. The tumor cells were arranged in the nest, possessing abundant eosinophilic cytoplasm. The tumor cell nuclei were round to oval with finely distributed chromatin and a small nucleolus. The foci of necrosis, hemorrhage, and edema within the tumor were noted. The surgical margins of the specimen were free of disease.

Immunohistochemically, the tumor cells showed diffuse membrane positivity for CD99, synaptophysin, and focal positivity for pancytokeratin and S-100. Tumour was negative for desmine, DOG-1, CD34, WT1, chromogranin, myogenin and OCT 4. Ki 67 was 30%. Overall the immunohistochemistry profile suggested the diagnosis of pPNET. The search for translocations had not been performed in our patient due to the unavailability of a molecular genetics platform in our hospital.

The postoperative course was unremarkable. The case was discussed in multidisciplinary meeting where it was decided to perform adjuvant chemotherapy based on Vincristine, Adriamycin, Cyclophosphamide (VAC) alternating with

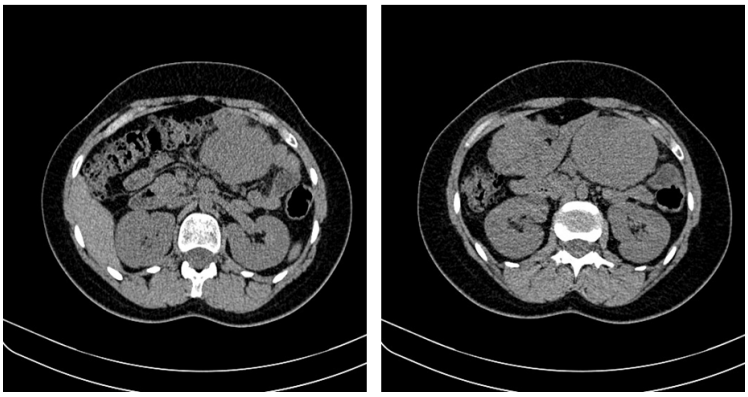

Figure 1. Computed tomography scan of the abdomen in axial section showing the ileal tumor process.

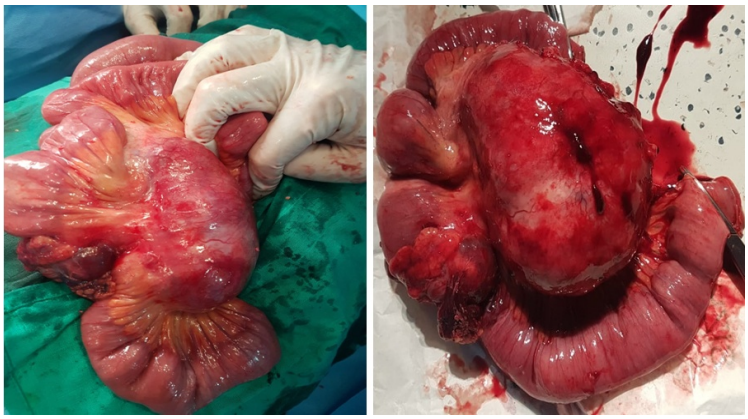

Figure 2. Operative image of the ileal resection.

Ifosfamide and Etoposide (IE). The patient received 6 cycles of chemotherapy with good tolerability. As the surgical procedure was considered curative, the radiotherapy supplement was not indicated.

She is currently alive 12 months after the chemotherapy, the clinical, biological and CT scanning examination did not show signs of recurrence.

3. Discussion

Ewing's tumors are malignant tumors characterized by small, round, blue cells that may show varying degrees of neuronal differentiation. Initially identified by James Ewing as being derived from endothelial cells, cytogenetic data showed that, in reality, this tumor was only an undifferentiated form of the neuroectodermal tumor family, and is currently referred to as the PNET tumor entity [9].

PNET/ES tumors are the second most common cause of malignant bone tumors in adolescents and young adults. These tumors mainly affect bone but can also be purely extraosseous in soft tissue [10] [11]. More rarely, visceral sites including the pancreas, liver, adrenal gland, esophagus, uterus, gastrointestinal tract, heart, kidneys, ovaries, testes, bladder and parotid gland have been described [12] [13] [14]. ES/PNETs of the small intestine are rare, to date only 35 cases have been reported in the literature (**Table 1**).

Table 1. Cases of ES/pPNET of the small bowel, reported in the literature to date.

Reference	Age/sexe	Localisation	Clinical presentation	Treatment	Metastasis ondiagnosis	Survival
Hori and Kato 2000 [15].	40/M	Jejunum	Intestinal perforation	Surgery/CMT	ND	5
Sarangarajna, *et al.* 2001 [16].	13/M	Jejunum	Occlusion	Surgery	Absent	12 NID
Shek, *et al.* 2001 [17].	9/F	Small bowel	Abdominal distension	Surgery/CMT	Pelvis	25
Adair, *et al.* [7].	21/f	Duodenum	Surgery/CMT	ND		10 NID
Graham, *et al.* 2002 [18].	14/M	Ileum	Anemia	Surgery/CMT	ND	52 NID
Balasubramanian, *et al.* 2002 [19].	53/F	Ileum	Abdominal Mass	Surgery	ND	ND
Kie, *et al.* 2003 [20].	20/F	Duodenum	ulcer	Surgery/CMT		18 NID
Boehm, *et al.* 2003 [21].	18/M	Ileum	Occlusion	Surgery/CMT	Peritoneum	ND
Bala, *et al.* 2006 [22].	57/F	Ileum	Mass	Surgery/CMT	ND	8 NID
Batzioui, *et al.* 2006 [23].	66/M	Small bowel		Surgery/CMT	ND	48 NID
Kim, *et al.* 2007 [24].	63/M	Ileum	Occlusion	Surgery/CMT	Lymph nodes	ND
Sethi and Smith 2007 [25].	44/M	Ileum	Occlusion	Surgery/CMT	ND	13
Rodarte-Shade, *et al.* 2012 [26].	32/M	Ileum	Anemia	Surgery/CMT	Absent	6 NID
Vignali, *et al.* 2012 [8].	15/F	Ileum	Mass	Surgery/CMT	ND	ND
Prasertvit, Stoikes 2013 [27].	28/F	Small bowel	ND	ND	ND	ND
Kim, *et al.* 2013 [28].	23/M	Jejunum	Tumor rupture without perforation	Surgery/CMT	Liver and lymph nodes	ND
Rachan Shetty 2014 [29].	24/M	Ileum	Occlusion	Surgery/CMT	ND	15 NID
Milione, *et al.* 2014 [30].	18/M	Ileum	Liver metastasis	ND	Liver	8
Milione, *et al.* 2014 [30].	20/M	Ileum	Liver metastasis	ND	Liver	28
Milione, *et al.* 2014 [30].	42/M	Ileum	ND	Surgery/CMT	absent	11
Milione, *et al.* 2014 [30].	45/M	Ileum	ND	Surgery/CMT	absent	13
Milione, *et al.* 2014 [30].	15/F	Ileum	ND	Surgery CMT/RTH	absent	28
Milione, *et al.* 2014 [30].	57/M	Ileum	ND	Surgery	absent	ND
Milione, *et al.* 2014 [30].	28/F	Ileum		Surgery	Liver	204 NID
Padma, *et al.* 2015 [31].	22/F	Jejunum	Mass	Surgery	absent	ND
Peng, *et al.* 2015 [32].	59/M	Ileum	Abdominal pain	Surgery	ND	ND
Peng, *et al.* 2015 [32].	22/M	Ileocecum	Mass	Surgery	Liver	ND
Peng, *et al.* 2015 [32].	36/F	Ileocecum	Mass	Surgery/CMT	ND	34
Liu, *et al.* 2016 [33].	15/M	Jejunum	Hematemesis, Melena, anemia	Surgery	ND	7
Li, *et al.* 2017 [34].	16/F	Ileum	Anemia	Surgery	ND	10 NID
Kim, *et al.* 2017 [35].	9/F	Jejunum	Anemia	Surgery/CMT	Peritoneum	ND
Liao, *et al.* 2018 [36].	25/F	Ileum	Mass	Surgery	ND	ND
Cantu, *et al.* 2019 [37].	67/F	Jejunum	Abdominal pain + constipation	Surgery	absent	3 NID.
Yagnik, *et al.* 2019 [38].	42/M	Jejunum	perforation	Surgery/CMT	ND	9 NID
Andrej, *et al.* 2020 [39].	30/F	Jejunum	asthenia	Surgery	absent	2
Our case	26/F	Ileum	Abdominal pain, transit disorder	Surgery/CMT	absent	No recurrence at 12 month.

M: Male; F: female; CMT: chemotherapy, RTH: radiotherapy, ND: not documented; NID: No information of death.

Among the reported cases, including our case, there were 19 males and 17 females. The mean age of the patients at diagnosis was 31 years for both sexes, with extremes ranging from 9 years to 67 years. The most frequent location in the small bowel was: ileum in 22 cases followed by jejunum in 9 cases followed by duodenum in 2 cases, in 3 cases the exact location in the small bowel was unspecified.

The clinical symtomatology is poor, dominated by locoregional signs related to the mass syndrome (pain, palpable mass) [8] [19] [22] [31] [32] [36]. Complications such as occlusion, perforation or rupture may occur [15] [16] [21] [24] [25] [28] [38]. Ileal PNET may be revealed by metastasis in advanced stages of the disease [30]. In the cases reported the most frequent metastatic location was in the liver.

Imaging examination such as CT scan can provide important information regarding the size of the mass, involvement of adjacent structures, and the presence of metastasis. However, there are no specific radiologic signs of PNET. For this reason, Ewing's sarcoma can initially be treated as a malignant gastrointestinal stromal tumor [22]-[34].

Diagnosis is always based on histological analysis and immunohistochemical study, supplemented or not by cytogenetic study.

Macroscopically, the tumor is rounded, oval or multi-nodular, well-limited, without encapsulation. When cut, it is grey-beige or yellow and its consistency is soft or friable. Necrotic or hemorrhagic reshaping is frequent. Calcifications are sometimes observed [40].

Histology shows a malignant proliferation of pseudo-alveolar or diffuse lobular architecture, consisting of small round or oval cells with monomorphic and poorly differentiated appearance. Occasionally, neural differentiation elements such as Flexner-Winsersteiner rosettes or Homer-Wright pseudo-rosettes are present. These elements indicate neuroectodermal origin, but their absence does not exclude diagnosis [41].

The differential diagnosis is first made with other round cell tumors: GIST, lymphoma, desmoplastic small round cell tumor and rhabdomyosarcoma. In this case, our patient was initially diagnosed with GIST due to clinical symptoms and imaging results.

Immunohistochemistry is of great help in distinguishing between these different tumor entities. Almost all Ewing/PNET tumors are positive for anti-CD99 antibody. However, it is not specific at all: CD99 membrane positivity is classical in lymphoblastic lymphomas, in very rare extramedullary myeloid tumors, in poorly differentiated round cell synovialosarcomas, desmoplastic tumors, and alveolar rhabdomyosarcomas are CD99+ [42]. Neuroectodermal markers are variably expressed and can be demonstrated in immunohistochemistry by the positivity of NSE, LEU7, synaptophysin, chromogranin, S100, and GFAP antibody. It is important to be aware of the possibility of labelling with anti-pankeratin AE1/AE3 antibody in about 25% of cases [43]. Desmin is exceptionally expressed

[44].

Two types of translocations predominate: translocations combine the N-terminal region of the EWS gene of chromosome 22 with the C-terminal region of a gene comprising the ETS sequence (FLI1 gene of chromosome 11 in 85% of cases or ERG of chromosome 21 in 10% of cases). Rarer translocations have been described as t (7; 22), t (17, 2), t (2, 22) translocations. These translocations are a true genetic marker of the PNET/Ewing entity [45].

In the absence of a therapeutic consensus on these exceptional tumors, the treatment remains the same as that proposed in other Ewing sarcoma localizations. The treatment of these tumors is based on a multimodal treatment combining local surgery and/or radiotherapy followed by multidrug systemic chemotherapy [31] [32] [33] [34]. Current chemotherapy regimens include combinations of vincristine, cyclophosphamide and doxorubicin [32]. The addition of ifosfamide and etoposide to a standard regimen significantly improves the outcome for patients with non metastatic Ewing's sarcoma a [45].

The prognosis remains difficult to predict due to the small number of reported cases and the lack of follow-up.

4. Conclusions

PNET of the ileum is an exceptional extraosseous malignant tumor. The therapeutic challenge of this disease is to ensure both systemic and local disease control.

The current treatment of these tumors is based on a multimodal treatment combining systemic chemotherapy, surgery and radiotherapy.

The prognosis is largely conditioned by the metastatic or localized stage.

Authors' Contributions

All authors have been involved in the process of writing and have approved the final manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

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