CASE REPORT

Myeloid sarcoma of the small intestine in a patient without overt acute myeloid leukaemia: a challenging diagnosis of a rare condition

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SUMMARY

Myeloid sarcoma (MS) is a rare condition that most commonly occurs in the setting of acute myeloid leukaemia (AML) or other chronic myeloproliferative disorders. It presents as an abnormal growth that can develop anywhere in the human body, and its clinical manifestations are often non-specific. We present the case of a patient admitted to the emergency room with bowel obstruction. After careful clinical assessment, she underwent a right hemicolectomy. After a thorough examination of the surgical pathology specimen, including testing a wide array of immunohistochemical markers, the patient was timely diagnosed with MS, allowing for the implementation of the appropriate treatment to achieve complete remission. This is crucial, since non-leukaemic patients with untreated MS always progress to AML, and have a better prognosis if adequate therapy is implemented early. Our patient is now in the second postoperative year and shows no signs of relapse.

BACKGROUND

Myeloid sarcoma (MS), also known as granulocytic sarcoma or chloroma, consists of a solid tumour of immature myeloid cells and/or myeloid blasts that develops in an extramedullary site. This rare condition occurs in three different situations: (1) in cases of acute myeloid leukaemia (AML); (2) chronic myeloproliferative disorders with impending blast crisis or indicating leukaemic transformation; (3) in rare cases, as an isolated tumour, preceding AML.^{1,2} This last group of patients, if left untreated, will progress to full-blown leukaemia within an average of 11 months.³

MS has been diagnosed in virtually every anatomical site. According to a review of 72 cases in the literature by Yamauchi and Yasuda,⁴ MS develops more commonly in lymph nodes (15%), skin (14%) or in the head and spinal cord (11%). This same review also reports 14 cases of MS occurring in the gastrointestinal (GI) system: 11 in the small intestine, one in the stomach, one in the liver and one in the pancreas. Another review focused on MS of the small bowel³ suggests that within this organ, the ileum is the most frequent location (65%). Even so, MS of the small intestine remains an exceedingly rare phenomenon, accounting for only 3 of 10 945 cases reported in a recent population study of small intestinal cancer in the USA.⁵ Moreover,

its clinical manifestations are non-specific, further confounding the diagnosis, particularly in patients without abnormalities in blood or medullary examinations. The most frequent symptoms are abdominal pain, constipation, GI bleeding or abdominal mass.⁶

In this article, we report a case of a primary MS of the distal ileum presenting with GI symptoms without any overt haematological condition.

CASE PRESENTATION

A 42-year-old woman was admitted to the emergency room, presenting with a colic-like abdominal pain for the past 3 months that had become worse since that morning and was now accompanied by several biliary vomiting episodes. She denied constipation, fever or any other symptoms. On examination, the abdomen was slightly distended and diffusely tympanic at percussion. Deep palpation aroused generalised pain without guarding or rebound tenderness. Auscultation of the abdomen revealed enhanced peristaltic movements. The patient had no relevant medical history. She had already sought help from a gastroenterologist; an upper GI endoscopy revealed no abnormalities, two total colonoscopies showed no alteration aside from a small sessile polyp 45 cm from the anal verge, an abdominal ultrasonography was normal and there were also no abnormalities in blood or urine tests.

INVESTIGATIONS

Blood tests revealed only a slight elevation in lactate dehydrogenase (335 U/L; normal range: 125–220 U/L), with no other abnormalities detected, including a normal complete blood count. The abdominal X-ray showed several hydroaerial levels of the small bowel. An abdominal ultrasound scan (figure 1) revealed a paretic loop of the small bowel in the right iliac fossa, with thickened walls and an image suggesting intussusception; dilation of small bowel loops in the right iliac fossa and right lumbar region and a mild peritoneal effusion. An abdominal CT scan was performed (figure 2), revealing marked distension of the small bowel caused by an abnormal mass in the terminal ileum, described as a 5 cm long area of wall thickening and stenosis. Several small lymph nodes were identified in the adjacent mesentery, and a mild peritoneal effusion was detected.

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Figure 1 Abdominal ultrasound scan: thickened bowel loop with target sign (arrow mark).

DIFFERENTIAL DIAGNOSIS

In the absence of any haematological abnormalities detected in blood tests, the diagnosis of MS is particularly challenging and the differential diagnosis will differ widely depending on the location and initial symptoms caused by the tumour. In the particular case of small bowel MS, the presenting symptoms are more commonly attributed to other relatively more common neoplasms of the small intestine such as undifferentiated carcinomas, non-Hodgkin's lymphomas or small round cell tumours.⁷ There is even at least one reported case of MS of the small intestine that was initially diagnosed as a Crohn's disease flare⁶ and another that presented as a case of chronic secretory diarrhoea with hypokalaemia and weight loss.⁸

Even after tumour resection, the correct histological diagnosis of MS remains difficult. As many as 47%–56% of tumours are initially misdiagnosed as other malignant lymphoproliferative disorders.^{3,4} It is important to bear in mind, though, that in the case of MS an early and accurate diagnosis has been correlated with better outcome and survival rates,⁶ hence the importance of applying other histochemical and immunological techniques

Figure 2 Abdominal CT scan: 5 cm lesion in the terminal ileum, causing intussusception (arrow marks).

Figure 3 Peroperative photo (arrow pointing at the lesion).

when assessing the aetiology of a small bowel mass of unknown origin, particularly in non-leukaemic patients. The immuno-histochemical analysis should test immunoreactivity to more specific markers such as myeloperoxidase, CD43 and CD45, for example, and at the same time should exclude reactivity to other lymphoid markers, in order to rule out the diagnosis of more frequent non-Hodgkin's lymphomas.⁹

TREATMENT

Facing a case of acute bowel obstruction caused by a tumour in the terminal ileum detected in a CT scan, the decision was made to perform an exploratory laparotomy. A large vegetative circumferential lesion, 4 cm wide, was found in the terminal ileum, located 7 cm from the ileocecal valve (figure 3). The patient was then subjected to a right hemicolectomy.

OUTCOME AND FOLLOW-UP

Histological analysis of the tumour revealed small neoplastic cells with round or folded nucleus and fine chromatin. The complementary immunohistochemical study showed strong immunoreactivity to CD45 (Leukocyte Common Antigen), myeloperoxidase, CD68, CD43 and Bcl2; and no immunoreactivity to CD20, CD79a, CD2, CD3, CD5, CD7, CD4, CD8, CD56, CD30, T-cell intracellular antigen, granzyme, CD23, C-kit, cyclin D1, CD10 and cytokeratin AE1/AE3. These features are consistent with the diagnosis of MS (figure 4).

Apart from perioperative periods of hypotension and superficial wound infection, there were no other major perioperative events.

The patient was discharged on postoperative day 18. Six weeks after the procedure, she was admitted to the haematology ward to begin systemic therapy. She underwent a full body fluorodeoxyglucose-18 PET/CT scan (figure 5) that excluded systemic involvement, and a bone marrow biopsy (figure 6) that also showed no signs of disease.

At the time of submission of this article, she is in the second postoperative year. She underwent a cycle of 7 days of cytarabine and 3 days of idarubicin, and three cycles of consolidation with high-dose cytarabine. She is currently asymptomatic and shows no signs of disease in a recent PET/CT-scan and medullary examinations. She remains under close surveillance in regular haematology consultations.

Figure 4 Pathology: (A) Macroscopy. (B–F) Microscopy: H&E stain 400x (B), myeloid cells with strong immunoreactivity to LCA 100x (C), myeloperoxidase 100x (D), CD68 100x (E) and CD34 100x (F).

DISCUSSION

Small bowel tumours represent only a small fraction of all GI tumours (1%–2%).⁶ Most commonly, they involve the ileum and are mostly of neuroendocrine origin (39%), carcinomas (31%) or lymphomas (18%).⁶ In a broad population study published recently, MS represent under 0.03% of all of the small intestinal tumours⁵ and have an incidence of 2 in 1 000 000 adults and 0.7 in 1 000 000 children.¹⁰ MS of the small bowel appears to be more common in male patients (85%), presenting in a mean age of 43 years (ranging from 8 to 69 years).³

Not only is MS a remarkably rare condition, it also poses a challenging diagnosis, particularly in the absence of abnormal haematological findings. This is one of the most important issues regarding MS, since its accurate diagnosis has a direct impact on the timely prescription of the appropriate treatment which is a cornerstone to achieve complete remission. As we have already stated, many cases of MS are misdiagnosed as other lymphoproliferative disorders, particularly if there is no blood or bone marrow involvement. It is not uncommon for MS tumours to display features mimicking those of lymphomas—most commonly high-grade non-Hodgkin's lymphomas—presenting no morphological evidence of granulocytic differentiation.⁴ Therefore, the employment of techniques such as histochemical and immunological staining, fluorescent in situ hybridisation, cytogenetic or flow cytometry becomes imperative for the accurate diagnosis of MS.

The most important immunohistochemical markers of MS include myeloperoxidase, CD117, CD99, CD43, lysozyme, CD68, CD34 and terminal-desoxynucleotidyl-transferase.^{11 12} Non-Hodgkin's lymphomas may also express some leucocyte antigens that are also immunochemical markers for MS, such as CD43 and CD45 (LCA); however, they are also stained by markers that are not present in MS tumours, like CD20 and

Figure 5 ¹⁸F-FDG PET/CT scan without evidence of suspicious lesions.

CD3.¹² Furthermore, blastic NK cell lymphomas persistently express CD43, CD56 and CD4, but are not stained by markers for myeloperoxidase, CD33, CD117, lysozyme and CD68, all of which are commonly found on MS tumours. These examples underline the importance of a complete immunohistochemical workup for the diagnosis of MS.¹²

Some chromosomal abnormalities have also been linked to the development of MS: monosomy 7, trisomy 8, mixed lineage leukaemia-splitting, t(8;21)(q22;q22) and inv(16).^{11 12}

Regarding available treatment options for MS, several studies have emphasised the superiority of systemic chemotherapy—a cytarabine-based anti-AML regimen, such as the treatment prescribed to our patient—when compared with radiation therapy or surgical resection alone. One study⁴ revealed that the progression from MS to full blown leukaemia was delayed by a mean of 30 months in patients treated with chemotherapy when compared with those left untreated.¹³ A review of treatment choices in 74 reported cases of MS reported that patients with non-leukaemic MS who underwent systemic chemotherapy remained leukaemia-free for a longer period (median: 12 months) when compared with those who were solely subjected to surgical treatment (median: 3 months) or radiation therapy (median: 6 months). Combining haematopoietic stem cell transplantation with systemic chemotherapy seems to improve event-free survival when compared with chemotherapy alone.² In a study published in 2004, Breccia

Figure 6 Bone marrow biopsy showing no signs of medullary involvement (May-Grünwald/Giemsa stain, 10x and 50x).

*et al*¹⁰ stressed the importance of a timely accurate diagnosis of MS; results showed that complete remission of both MS and leukaemia was only achieved in patients who received systemic chemotherapy at least 4 months before the onset of overt leukaemia. No patient treated after this threshold obtained complete remission at the bone marrow level even if the initial MS was fully treated. Tsimberidou *et al*¹⁴ concluded that complete response to anti-AML chemotherapy was more promptly achieved by patients with MS (69%) than by patients with AML (54%). Event-free survival and overall survival rates in the course of 2 years were also better for patients with MS (32% and 43%, respectively) than for patients with AML (18% and 29%, respectively). These results further emphasise the advantages of an early implementation of systemic chemotherapy in patients with MS. Surgical treatment and radiotherapy should then be reserved for symptomatic therapy since it has not been proven that they improve overall survival or event-free survival rates.⁶ In the case presented here, surgical therapy was inevitable, not only for the urging need to relieve the acute obstructive symptoms, but also to allow an accurate diagnosis, through thorough immunohistochemical analysis of the resected tumour.

In summary, MS is an extremely rare condition that poses a challenge to accurately diagnose. Nevertheless, it should be always considered as a possible diagnosis in cases of tumours of the small bowel of unknown origin, even if no haematological

abnormalities are present at the time. This constitutes a crucial point for patients with MS, since it has been clearly demonstrated that early treatment with anti-AML systemic chemotherapy is associated with the best response and survival rates. Therefore, in these tumours, a complete immunohistochemical workup is imperative in order to correctly identify MS, avoid misdiagnosis as other lymphoproliferative malignancies, and proceed with their appropriate treatment.

Learning points

- Myeloid sarcoma (MS) is a rare condition that often presents as a set of unspecific mass-related symptoms; its diagnosis is dependent on a thorough pathological examination through the detection of specific immunohistochemical markers.
- The treatment of MS with cytarabine-based anti-acute myeloid leukaemia (AML) chemotherapy seems to be superior to surgical or radiation therapy alone; and complete remission can only be achieved if systemic chemotherapy is started within the first 4 months on diagnosis.
- Patients with MS tend to have a better response to chemotherapy than those with AML, achieving complete response more promptly and better event-free survival and overall survival rates.
- Therefore, even though MS is a quite rare condition, all patients with a suspicious mass should be screened for this disease through a careful pathological examination, in order to give them a better chance at achieving full sustainable remission.

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