Granulocytic Sarcoma of the Small Intestine

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• Granulocytic sarcoma is an extramedullary tumor of myeloblasts and/or immature myeloid cells, which can develop at any anatomic site and is often a forerunner to the development of acute myelogenous leukemia. Granulocytic sarcoma of the gastrointestinal tract most frequently involves the small intestine and most often presents with abdominal pain and obstruction. Pathologists must consider granulocytic sarcoma in any mass of unknown origin with a diffusely infiltrating population of tumor cells, as the diagnosis is often initially unrecognized, especially in nonleukemic patients. Multiple ancillary modalities are available to assist pathologists in making the correct diagnosis so that appropriate therapy can be initiated.

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Myeloid sarcoma represents an extramedullary tumor of myeloblasts and/or immature myeloid cells.[1] Previous terms used to describe this entity include extramedullary myeloid tumor, granulocytic sarcoma (GS), and chloroma. Chloroma was the initial term used to describe these neoplasms, due to the gross greenish appearance identified in some lesions.[2] The World Health Organization classification of hematopoietic tumors divides myeloid sarcoma into 2 major categories.[1] The more common form is GS, composed mainly of myeloblasts, neutrophils, and myeloid precursors. The less common form is monoblastic sarcoma, which is typically composed of monoblasts and is associated with acute monoblastic leukemia. Granulocytic sarcoma occurs in a variety of clinical settings and has been described in almost every anatomic location, with the gastrointestinal system representing a relatively common site. In this article, we review the clinical, gross, and microscopic features; differential diagnosis; and treatment of GS, especially with regard to small intestinal involvement.

CLINICAL FEATURES

Granulocytic sarcoma can present in multiple clinical settings and has been reported to occur in a variety of anatomic sites. It may present in association with acute myeloid leukemia (AML), either as an initial presentation or as a relapse. It may also signal impending blast crisis in the setting of a myeloproliferative disorder or leukemic transformation in myelodysplastic syndrome. Less commonly, it may also occur as an isolated mass in nonleukemic patients (primary GS). In this later setting, the majority (88%) of untreated patients progress to AML within 11 months.[3,4] Granulocytic sarcoma has a reported incidence of 2% to 7% in AML patients.[2,5] Granulocytic sarcoma in the setting of AML occurs most frequently in acute myeloblastic leukemia with maturation (French-American-British [FAB] M2) but has also been described in the other subtypes including FAB M0, M1, M3, M4, M5, and M7.[3,6] Granulocytic sarcoma occurring after allogeneic bone marrow transplantation has also been rarely described in patients treated for AML, myelodysplastic syndrome, and chronic myeloid leukemia. In 1 large series examining 5824 bone marrow transplantation patients, 26 (0.45%) developed GS 4 to 56 months posttransplantation, and 20 of these patients had been treated for AML.[6] These results suggest that a lower incidence of GS occurs in patients following transplantation.[6]

Granulocytic sarcoma has been reported to occur in about every anatomic location imaginable. The most common sites are the skin (13%–22%), bone/spine (9%–25%), and lymph nodes (15%–25%).[3,4] The gastrointestinal tract is also a relatively common location for presentation, and the most common clinical presentation is acute or intermittent abdominal pain from partial to complete bowel obstruction (Figure 1). Less frequent symptoms include nausea, vomiting, weight loss, fever, and gastrointestinal bleeding. The most frequently involved region of the gastrointestinal tract is the small intestine (10%–11%).[3,4,7] Other regions of the gastrointestinal tract that have been reported to be involved are the stomach and large intestine, including 2 cases of GS involving adenomatous polyps.[8] Only 4 cases involving the appendix have been identified.[9–11] In 1 of these case reports, the patient presented with symptoms consistent with appendicitis and was diagnosed initially with large cell lymphoma.[9] Six days later this patient presented with a partial small bowel obstruction of the terminal ileum, which was found to be GS.[9] Patients developing GS posttransplantation have a similar distribution of GS lesions; however, to our knowledge no cases involving the small intestine have been reported.[6] We have recently seen a case of GS that to our knowledge represents the only reported case of GS involving the small intestine in the setting of related donor peripheral stem cell transplant (Figures 1 through 4).

Granulocytic sarcoma may present as either isolated or multiple lesions involving 1 or more organ systems, and lesions may be synchronous or metachronous. In a larger series, the majority of reported cases presented as isolated masses (69%), whereas in patients with multiple lesions, up to 4 organ systems involved at one time were described.[3] In 1 case report, a patient with AML M2 in complete remission had a series of 11 periodic granulocytic sarcomas occurring during a 29-month period before succumbing to the disease.[12] Our case (Figures 1 through 4) had multiple lesions present throughout the small intestine, which to our knowledge has only been described previously in 1 reported case of GS of the small intestine.[13]

A number of cases of GS involving the small intestine have been reported in the literature (Table 1).[9,13–22] The age of presentation has ranged from 8 to 69 years (mean, 43 years), with the majority occurring in male patients (17/20 cases). In 11 (65%) of 17 cases, ileal involvement was

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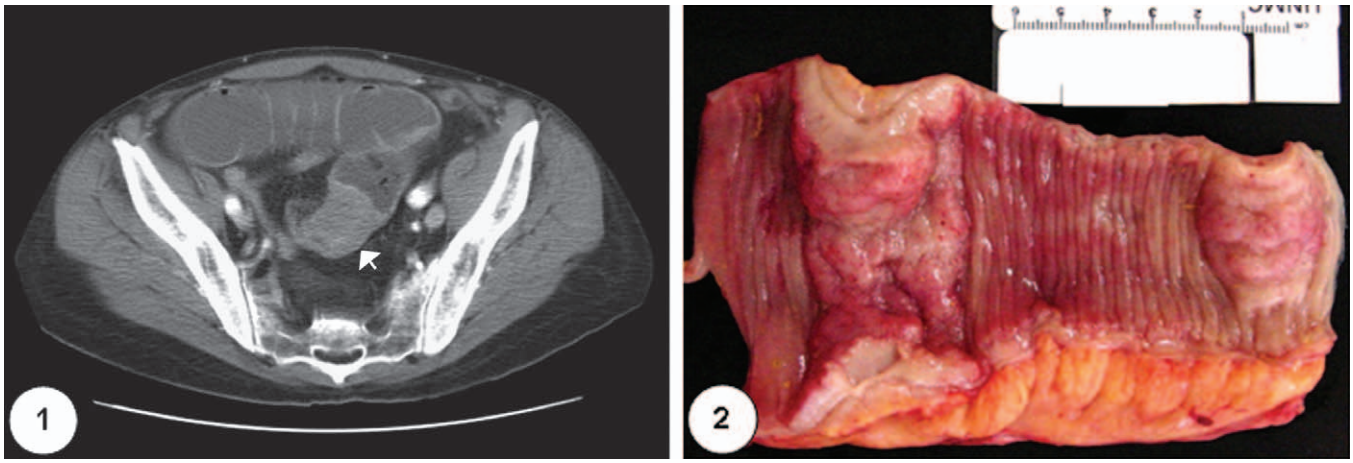

Figure 1. *Abdominal computed tomographic scan showing a 4-cm region of circumferential thickening involving the ileum (arrow). The patient is a 55-year-old man with a past medical history of acute myeloid leukemia M2 in complete remission diagnosed 2 years earlier and was status post allogeneic peripheral stem cell transplantation.*

Figure 2. *The resected 21-cm-long segment of bowel was found to contain 2 concentric exophytic masses measuring 9.0 × 8.0 × 4.5 (100% circumferential involvement) and 4.2 × 3.4 × 3.0 cm. The masses had soft, tan-white, "fish-flesh" cut surfaces.*

Summary of Clinicopathologic Features in Reported Cases of Granulocytic Sarcoma of the Small Intestine*

Case	Source, y	Age, y/Sex	Presentation	Location	Disease at Presentation	Outcome
1	Xavier et al[9], 2003	36/M	SBO, AP	Appendix, ileum, mesentery	10.4% blasts in BM	NED at 10 mo
2	Martinelli et al[10], 1997	45/M	SBO	Appendix, ileum, lymph nodes	AML M2 (7 mo later)	NED at 63 mo
3	Corpechot et al[13], 1998	57/M	SBO, peritonitis	Ileum	CML blast crisis	Death at 4 mo
4	Corpechot et al[13], 1998	57/M	SBO	Jejunum, lymph nodes	N/A	AML M2 at 2 mo
5	Corpechot et al[13], 1998	34/M	SBO	Ileum, mesentery	None	Postoperative death (sepsis)
6	Corpechot et al[13], 1998	64/F	SBO, diarrhea, fever	Jejunum	AML M2	Postoperative death (sepsis)
7	Corpechot et al[13], 1998	40/M	SBO	Jejunum	None	AML M2 at 21 mo
8	Meis et al[14], 1986	16/F	AP, distention	Small intestine, lymph nodes	None	NED at 72 mo
9	Meis et al[14], 1986	31/M	SBO, AP	Ileum, lymph nodes	None	AML at 8.5 mo
10	Russell et al[15], 1988	49/M	SBO, AP, WL, vomiting	Small intestine, lymph nodes	None	AML M4E0 at 3 mo
11	Beck et al[16], 1984	30/M	SBO, AP, vomiting	Ileum, cecum (10 cm)	None	NED at 67 mo
12	Julia & Nomdedeu[17], 2004	30/M	N/A	Small intestine	None	AML at 1 mo
13	Julia & Nomdedeu[17], 2004	38/M	AP, heartburn	Antrum, duodenum, jejunum	None	AML M4E0 at 8 mo
14	Brugo et al[18], 1977	38/M	SBO	Ileum (6 cm), lymph node	None	AML at 36 mo
15	Orlandi et al[19], 1989	52/M	Testicular mass, AP	Right testis, ileum	AML M2 in CR 66 mo	Postoperative death (sepsis)
16	Hamilton et al[20], 1992	53/F	AP, WL, vomiting	Duodenum, jejunum, ileum	AML M4EO	NED at 12 mo
17	Hamilton et al[20], 1992	52/M	Subacute SBO	Jejunum, lymph nodes	AML M4EO	Death from pulmonary emboli
18	Goh et al[21], 1985	69/M	SBO	Duodenum, jejunum	None	Postoperative death (sepsis)
19	Kowal-Vern et al[22], 1991	8/M	AP, vomiting	Ileum (10 cm), lymph nodes	None	NED at 48 mo
20	Present case	55/M	AP, vomiting	Multiple ileal masses	AML M4 in CR 2 years	NED at 23 mo

* SBO indicates small bowel obstruction, AP, abdominal pain; BM, bone marrow; NED, no evidence of disease; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; N/A, not available; WL, weight loss; and CR, complete remission.

identified. Most of the cases (12/16) occurred in nonleukemic patients, with 1 case occurring in chronic myeloid leukemia blast crisis.[13] Eight of the patients were reported to progress to AML within a mean of 10.8 months (range, 1–36 months). One mass developed in a 52-year-old man who had been in complete remission for AML M2 for more than 5 years.[19]

GROSS FEATURES

Granulocytic sarcoma of the gastrointestinal tract can have a variety of gross appearances including polypoid or exophytic masses, regions of wall thickening, and/or ulcerations (Figure 2). The lesions are typically pink to gray-white, and greenish discoloration has been described in only 1 case involving the stomach and regional lymph nodes.[18] Lesions as large as 10 cm in greatest dimension[16,22] or diffusely involving the antrum, duodenum, and jejunum have been described.[17] Regional lymph nodes (mesenteric and retroperitoneal) are frequently involved.

MICROSCOPIC FEATURES

The histologic features for most cases consist of a diffusely infiltrating population of medium to large cells with occasional prominent nucleoli and minimal to moderate eosinophilic cytoplasm (Figure 3, A and B).[4] Current classification systems further divide GS into blastic (mostly myeloblasts), immature (myeloblasts and promyelocytes), and differentiated (promyelocytes, myelocytes, and neutrophils) types based on the degree of myeloid maturation.[1] A variable number of admixed maturing eosinophils and neutrophils are typically present in the more differentiated lesions.[4,14] Eosinophilic myelocytes have been reported in up to 50% of cases and are felt to be a characteristic feature supporting the diagnosis of GS.[14]

Most tumors appear to be mitotically active, but the mitotic rate shows great variability between lesions with no correlation with the degree of maturation.[4,14] A variety of nuclear morphologic features have been described including irregularly shaped, folded nuclei; fine chromatin with inconspicuous nucleoli; and nuclei with bean-shaped, monocyte-like features, indicative of the monoblastic variant of GS.[4,14] Numerous tingible body macrophages and a ''starry-sky appearance'' can be seen.[4,14] Even though these tumors demonstrate diffuse sheets of infiltrating tumor cells, the lack of necrosis is a feature that can be helpful in differentiating GS from other neoplasms.[14]

DIAGNOSIS AND DIFFERENTIAL CONSIDERATIONS

The diagnosis of granulocytic sarcoma can be supported with the use of multiple modalities including histochemical and immunoperoxidase stains, conventional cytogenetics, fluorescent in situ hybridization cytogenetics, and flow cytometry. These techniques are especially important in primary GS, in which a previous diagnosis of leukemia or myelodysplastic syndrome has not been made. A significant proportion of tumors (47%–56%) are initially misdiagnosed as malignant lymphoproliferative disorders, Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, medulloblastoma, or poorly differentiated carcinomas.[1,3,7] In one larger series, the majority of misdiagnoses were associated with lesions categorized as ''blastic'' (62%).[4] The correct diagnosis can be derived with the aid of histochemical and immunoperoxidase stains such as naphthol–ASD–chloroacetate esterase, lysozyme, CD34, CD117, and myeloperoxidase (MPO) (Figure 4, A through C). The majority of lesions stain for either naphthol ASD chloroacetate esterase (75%–80%) or lysozyme (89%–90%).[4,7] In one study, 56 (98%) of 57 cases showed positive staining for at least 1 of these markers, and in 31 cases (54%), both were positive.[7] CD43 staining of tumor cells in the absence of CD3 staining should also prompt pathologists to consider a diagnosis of GS in a neoplasm of uncertain origin.[1] Other markers such as keratin, CD3, and CD20 are helpful in excluding carcinomas and lymphoproliferative disorders. Flow cytometry also is helpful in identifying blast populations expressing stem cell (CD34), myeloid (CD13, CD33, CD117, MPO), and/or monocytic (CD11c and CD14) antigens. As mentioned above, CD34 and CD117 are antigens that can also be assessed by immunohistochemistry and can be very useful in establishing the diagnosis when flow cytometry has not been performed.

Conventional cytogenetics and fluorescent in situ hybridization studies are probably most useful in identifying specific characteristics present in previous lesions as a sign of relapse or residual disease. Specific cytogenetic abnormalities most frequently associated with GS include t(8;21)(q22;q22) and inv(16)(p13q22), which have been reported in as many as 54% and 25% of cases, respectively.[5] Five cases of GS of the small intestine with 16q abnor-

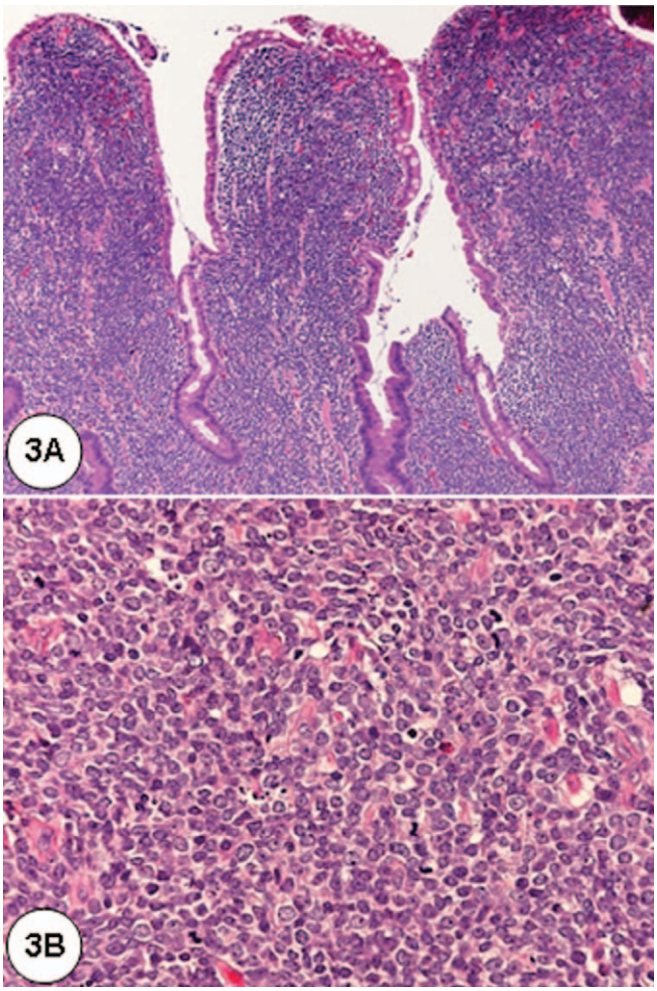

Figure 3. *Hematoxylin-eosin–stained sections showing a diffuse transmural cellular expansion of medium and large cells, with scant eosinophilic cytoplasm, vesicular nuclei, occasional nucleoli, and frequent mitosis. Rare neutrophils and eosinophils are also present (original magnifications ×100 [A] and ×400 [B]).*

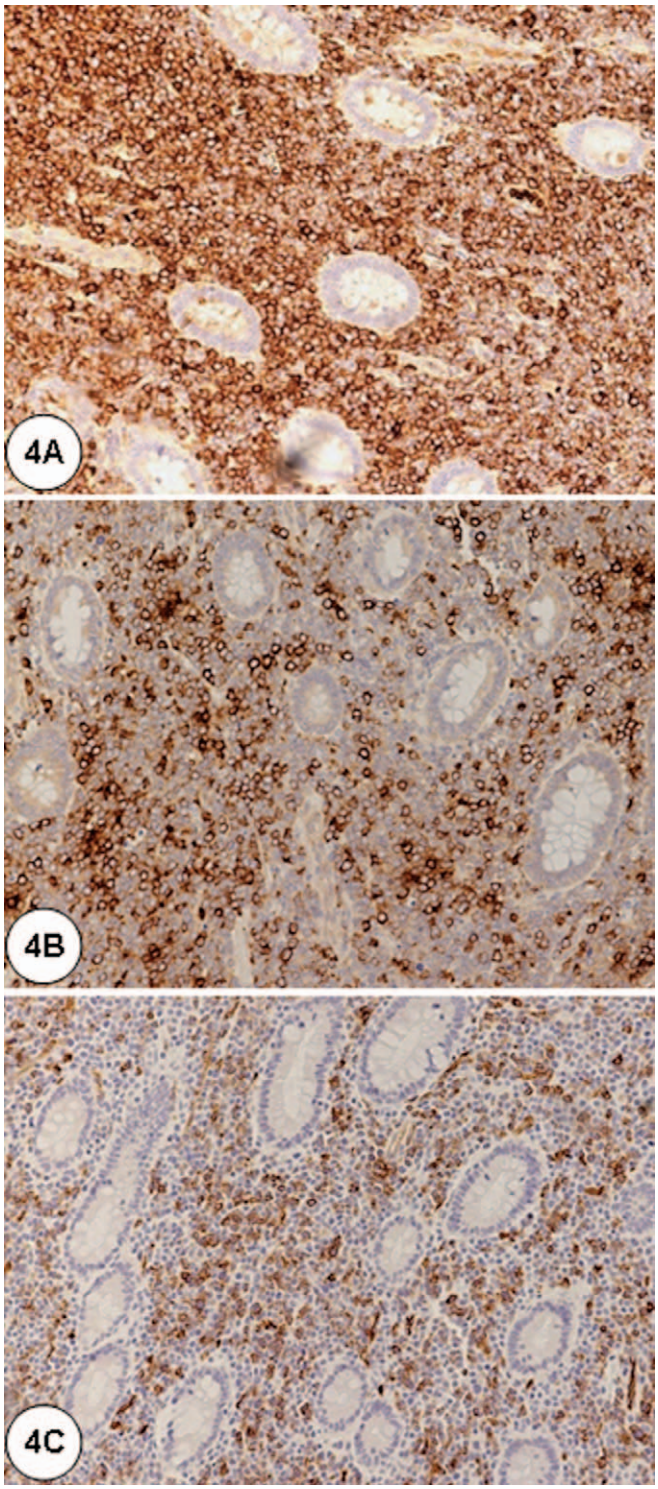

Figure 4. *Immunohistochemistry showing staining of the tumor cells for lysozyme (A) and CD34 (B) and focal staining for myeloperoxidase (C). Flow cytometry immunophenotyping of the mass confirmed a myeloblast population (original magnifications ×200).*

malities have been reported, further supporting these findings.[9,15,17]

TREATMENT AND PROGNOSIS

The prognosis of GS is variable but seems to be somewhat similar to that of AML.[5,10] Granulocytic sarcoma has been treated with systemic chemotherapy, surgical resection, radiation therapy, and peripheral stem cell/bone marrow transplantation. Although only a few large series comparing treatment modalities of GS are available in the literature,[4,5] systemic chemotherapy seems to offer the most benefit. One study compared treatment (surgical resection vs local radiation vs systemic chemotherapy) outcomes of 74 cases of primary GS with no transformation to AML within 1 month of diagnosis and found a significantly longer nonleukemic period in patients receiving systemic chemotherapy.[4] Eighty-one percent (26/32) of the patients who underwent surgical resection or local radiation therapy progressed to AML within 11 months,[4] which is similar to previously reported results (mean, 10.5 mo) in patients not receiving chemotherapy.[7] In this study, 58% (25/42) of the patients who received systemic chemotherapy remained disease free for more than 11 months, and 19% (8/42) did so for more than 2 years, compared to 5% (1/32) receiving no chemotherapy.[4] In addition, this same study showed that a significantly longer nonleukemic period occurred in patients receiving traditional chemotherapy (cytosine arabinoside and anthracycline) for AML than those receiving other agents (cyclophosphamide, vincristine, and prednisone) typically utilized for non-Hodgkin lymphoma.[4] These findings further emphasize the importance of correctly diagnosing GS. Peripheral stem cell/bone marrow transplantation has been performed in a few patients with GS in combination with systemic chemotherapy with positive results, but further studies will need to be performed to evaluate its effectiveness compared to systemic chemotherapy alone. One reported case of GS involving the ileum treated with surgical resection, systemic chemotherapy, and related allogeneic bone marrow transplantation occurred in an 8-year-old male patient.[22] The patient went into complete remission without relapse at 4 years.

CONCLUSIONS

Granulocytic sarcoma can develop in any anatomic site and often represents a forerunner to the development of AML in nonleukemic patients. Granulocytic sarcoma of the GI tract most commonly involves the small intestine and most often presents as abdominal pain and obstruction. Pathologists must consider GS in any mass with a diffuse infiltrating population of tumor cells, as the diagnosis is often initially unrecognized, especially in nonleukemic patients. Treatment should consist of systemic chemotherapy tailored to the treatment of AML, possibly in conjunction with surgical resection or radiation in appropriate clinical settings.

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