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Case Report

# Granulocytic Sarcoma Involving the Gynecologic Tract: One Case Report and Review of the Literature

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**Abstract**

Granulocytic sarcoma is an extramedullary tumor associated with acute myeloid leukemia (AML). It is rarely seen in the female tract. We report an unusual case of granulocytic sarcoma of the uterus in an AML patient who relapses after 14 years of first complete remission. A mixed-lineage leukemia (*MLL*) gene rearrangement supports the association of that malignancy with prior chemotherapy. Second line therapy consisted in chemotherapy, radiation, and allogeneic stem cell transplantation.

**Keywords:** Acute myeloid leukemia; Granulocytic sarcoma; Prognosis; Treatment; Gynecologic tract

## Introduction

Myeloid sarcomas are rare extramedullary tumors of immature myeloid cells. They comprise two major subtypes: granulocytic sarcomas composed of granulocytic precursors at various stages of differentiation and monoblastic sarcoma which consist of monoblasts and immature monocytes [1]. In the largest published series of myeloid sarcomas, 50% were of granulocytic type, 43.5% either monoblastic or myelomonoblastic, and 6.5% corresponded to different histotypes [2]. The lesion was first described by Burns in 1811 [3]. It was named 'chloroma' because it displays a greenish colour due to the presence of myeloperoxidase (or verdoperoxydase) [4] and was then found to be associated with acute myeloid leukemia (AML) [5,6]. The preferred term of 'granulocytic sarcoma' was coined later [7]. Myeloid sarcoma resembles a solid tumor and should not be confused with diffuse extramedullary leukemic infiltrates. It is most commonly diagnosed as part of the systemic manifestations of AML, and develops in 2-8% of patients with AML [8,9]. On rare occasions, it may also be the presenting symptom. Myeloid sarcoma may also be the sole manifestation of relapse of previously treated myeloid leukemia. Granulocytic sarcoma may occur at almost any body site. Involvement of the female genital tract is uncommon [10]. The most commonly involved organs are the ovary, the uterine cervix and the uterus corpus [11].

We report here one case of granulocytic sarcoma of the uterine cervix with extension to the left parametrium concomitant to bone marrow involvement in one patient treated 14 years earlier for AML.

## Case Presentation

A 44-year old woman (gravida 2, para 2) (with a past history of surgery for adenofibroma of the left breast in 1985) presented to our institution in October 2000 with fatigue, dyspnea, gingival hemorrhage, and menorrhagia. Clinical examination was normal. Blood test displayed white blood cell count at 2.4 x $10^9$/L with 18% neutrophils and 60% circulating blasts, anemia, and thrombocytopenia. Bone marrow aspirate confirmed the diagnosis of FAB M1-AML with medullary infiltration by 40% of blastic cells of which 25% with Auer rods. Cytogenetic studies showed 46, XX [17]/46, XX, add (21) (q21-22) [3]. Molecular analyses were negative for *mixed-lineage leukemia (MLL)* rearrangement; *CEBPa*, *FLT3*, and *NPM1* mutations; and *WT1* overexpression. After given written informed consent, she was included into the ALFA 9802 trial [12]. Induction chemotherapy regimen consisted of a timed sequential chemotherapy with a first sequence combining daunorubicin (80 mg/$m^2$/d on days 1-3) and cytarabine (500 mg/$m^2$/d over the same period) and a second sequence, administered after a 4-day free interval, with mitoxantrone (12 mg/$m^2$/d on days 8 and 9) and cytarabine (500 mg/$m^2$/12h on days 8-10). After complete remission (CR) achievement, she was assigned to consolidation chemotherapy, despite one HLA-compatible sibling, in the absence of risk factors. She received 4 cycles of high-dose cytarabine (3 g/$m^2$/12h on days 1, 3, and 5) followed by 4 additional maintenance courses (daunorubicin, 45 mg/$m^2$ on day 1, and cytarabine, 100 mg/$m^2$/12h on days 1-5). During chemotherapy, she received granulocyte-macrophage colony-stimulating factor as priming, and lynestrenol was prescribed once daily as prophylaxis against menorrhagia.

After 14 years without any symptoms, she presented again in January 2015 with lumbar pains and functional and obstructive urinary signs, suggesting symptoms in relationship with kidney stone. Sonographic evaluation of the pelvis revealed left ureteropyelocaliceal dilatation. Urinary tract double-J stent was positioned to facilitate the upper urinary tract drainage. CT and magnetic resonance imaging (MRI) scans performed by February 2015 showed an increase in size of the uterus cervix with a tumor of 4 cm of largest diameter and multifocal heterogeneous low signal intensity lesions from the upper vagina to the left parametrium, which suggested a malignant infiltrative process (Figure 1). A pelvic examination confirmed hypertrophy of the cervix. Histopathological examination of multiple colposcopic biopsies of the uterine cervix revealed an infiltration by proliferative, round, small immature myeloid cells among stromal cells (Figure 2). The immunophenotypic study showed that malignant cells expressed vimentin, CD56, CD117, myeloperoxidase, CD43, and CD34, and confirmed the diagnosis of granulocytic sarcoma. Positron emission tomography (PET) scan imaging performed on March 2015 showed hypermetabolism of the cervical mass contiguous with a large left parametrial mass that displaced the left ureter. This was




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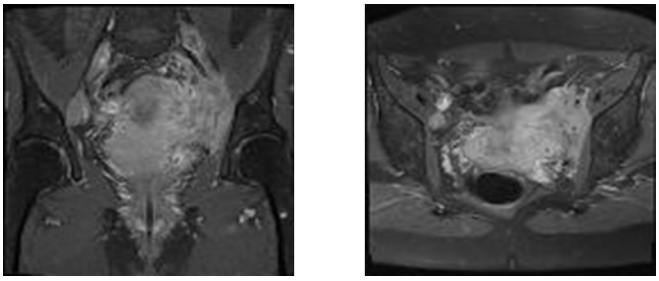

**Figure 1:** Axial T2 weighted pelvic MRI imaging showing lesions from the upper vagina to the left parametrium, which suggested a malignant infiltrative process.

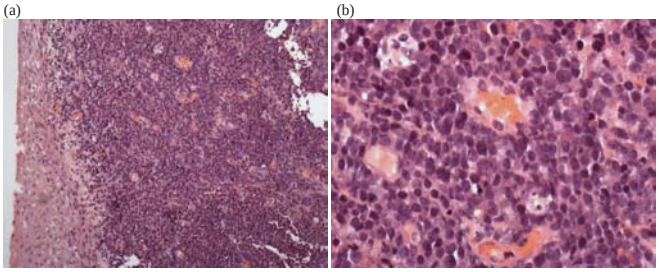


**Figure 2:** Biopsy from uterine cervix. Diffuse infiltration by immature myeloid blastic cells; a finding compatible with granulocytic sarcoma: (a) x20; (b) x40.

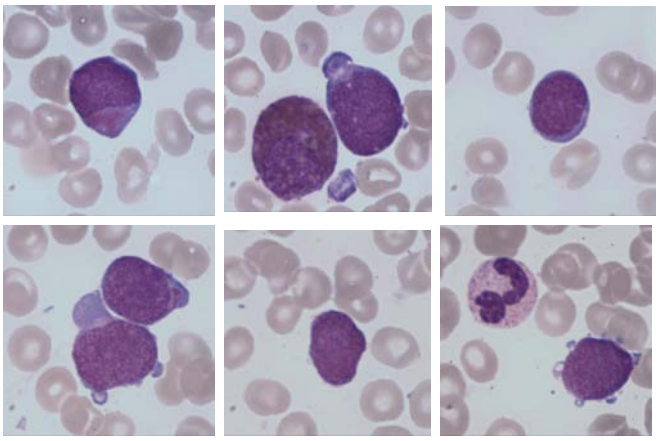

**Figure 3:** Hematological relapse with poorly differentiated myeloid blastic cells (MGG x100).

associated with hypermetabolic tumor infiltration of the left iliac axis and hypermetabolic activity in right iliac, aortico-lumbar and inters-aortico cave adenopathies.

The patient was hospitalized in the Hematology Department by the end of March 2015. There were no palpable lymph nodes and no hepatosplenomegaly. Laboratory studies revealed the following values: hemoglobin 107 g/L, platelets 228 x $10^9$/L, white blood cells 4.42 x $10^9$/L with 2.65 x $10^9$/L neutrophils and, at that time, no abnormal cells. Bone marrow examination showed an infiltration by 40% of poorly differentiated myeloid blastic cells (Figure 3) ($CD34^+CD38^+/CD123^{++}$, $CD13^+CD33^+CD117^+$) combined with a minor lymphoblastic B CD20-negative sub-clone. Cytogenetics of the bone marrow revealed a normal female karyotype. A duplication of the

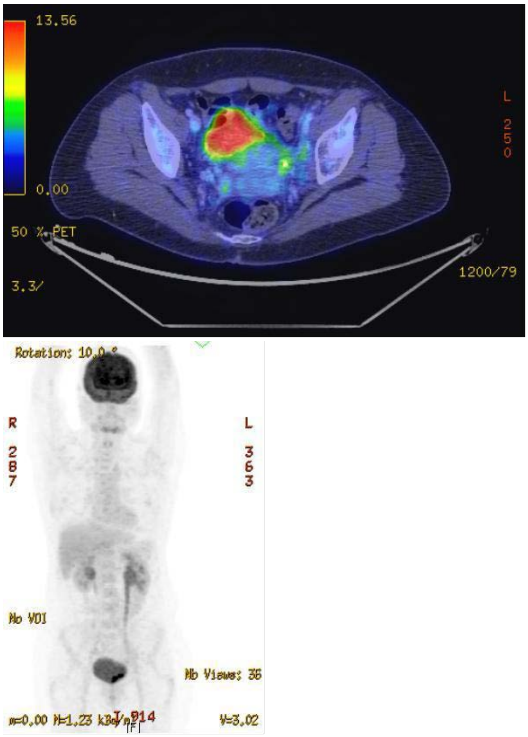


**Figure 4:** PET scan taken on 30th day of induction therapy showing the persistence of only two hypermetabolic sites in the bladder.

*MLL* gene was identified by molecular biological analysis. The patient received re-induction chemotherapy combining idarubicin (10 mg/$m^2$/day for 3 days) and intermediate-dose cytarabine (1 g/$m^2$/12h for 6 days) [13]. Bone marrow aspirate performed at day 32 confirmed the achievement of a complete medullary response. Post induction chemotherapy PET scan taken on 30th day of treatment showed that the uterine mass had been resolved. Only two hypermetabolic sites persisted in the bladder: one located on the left ureteral meat us and the other one on the left lateral side (Figure 4).

Consolidation chemotherapy consisted of high-dose cytarabine (3g/$m^2$ x 2/day for 3 days). PET scan controlled after recovery from aplasia showed the absence of hypermetabolic sites. The residual density in the left parametrium was consistent with scar tissue. Consolidation chemotherapy was followed by radiotherapy of the pelvis of 24 Gy in 12 fractions of 2 Gy. Allogeneic peripheral blood stem cell transplantation from a HLA-matched sibling donor was performed on August 6th, 2015 after reduced-intensity conditioning regimen (cyclophosphamide 60 mg/Kg, busilvex 3.2 mg/Kg/d for 2 days, and anti-thymocyte globulins for 3 days) following FLAMSA chemotherapy (fludarabine 30 mg/m2/d, amsacrine 100 mg/m2/d, and cytarabine 2 g/m2/d for 4 days) [14].

## Discussion

Granulocytic sarcoma estimated incidence is about 2 per million in adults [15]. The mean age at presentation is 47 years [16]. Although asymptomatic disease appears relatively common at autopsy, symptomatic involvement of the female genital tract is a rare presentation of extramedullary AML. Uterus and ovary are the most frequent sites of gynecologic tract involvement. Symptoms of

**Table 1:** Review of the literature regarding myeloid sarcoma involving the female genital tract.

| Reference | Site | AML Previous/concurrent | Age | Treatment |
|---|---|---|---|---|
| [42] | Uterine cervix | No/Yes | 26 | None |
| [43] | Uterine cervix | No/NS | 39 | Rad |
| [44] | Uterine cervix, ovary | Yes/Yes | 50 | TAH-BSO, Chemo |
| [26] | Vagina | Yes/No | 13 | Chemo |
| [45] | Uterine cervix | No/No | 44 | TAH-BSO |
| | Uterine cervix | No/No | 75 | Rad |
| | Ovary | No/NS | 37 | SO, Chemo |
| [46] | Ovary | No/No | 28 | SO |
| [47] | Ovary | No/No | 44 | SO |
| [24] | Vulva, vagina | No/Yes | 24 | Steroids |
| [48] | Uterine cervix | No/No | 65 | Rad |
| [25] | Vulva, vagina | No/Yes | 45 | Chemo |
| [49] | Uterine cervix | No/Yes | 58 | None |
| [50] | Ovary | Yes/Yes | 18 | Chemo |
| [51] | Uterine cervix | No/Yes | 36 | TAH-BSO |
| [52] | Ovaries | No/Yes | 1 week | SO, Chemo |
| [53] | Uterine cervix | No/No | 39 | None |
| [27] | Vagina | Yes/Yes | 34 | Chemo, Rad |
| [54] | Uterine cervix | No/Yes | 59 | None |
| | Uterine cervix | No/No | 59 | Rad |
| [55] | Uterine cervix | No/No | 40 | Chemo, Rad |
| | Uterine cervix | No/No | 48 | TAH-BSO, Chemo |
| [56] | Uterine cervix | No/No | 34 | Chemo |
| [57] | Uterine cervix | Yes/No | 33 | None |
| [58] | Vagina | Yes/No | 53 | Chemo, Rad |
| [40] | Uterine cervix | No/No | 43 | Chemo |
| | Uterus, adnexal | No/No | 17 | Rad |
| [59] | Adnexal tumor | Yes[b]/Yes | 36 | Steroids |
| [60] | Uterine cervix | No/No | 32 | Rad |
| [61] | Uterine cervix | No/No | 66 | Chemo |
| [62] | Ovary | No/Yes | 46 | None |
| [63] | Ovary | No/No | 49 | NS |
| [17] | Uterine cervix | No/Yes | 51 | Chemo |
| [64] | Ovary | No/No | 31 | Chemo |
| [65] | Uterine cervix | No/No | 48 | Chemo |
| [33] | Ovary | No/Yes | 17 | Chemo, oophorectomy |
| | Ovary, omentum | No/Yes | 46 | Exploratory laparotomy, Chemo |
| [66] | Uterine cervix | No/No | 20 | Chemo, hysterectomy, AutoSCT, Rad |
| [67] | Uterine cervix | Yes/Yes | 35 | Chemo |
| [68] | Uterine cervix | No/No | 33 | Death before treatment |
| [11] | Ovaries | No/No | 30 | Bilateral oophorectomy |
| | Ovary | No/No | 31 | Oophorectomy, omentectomy, Chemo |
| | Ovary | No/No | 31 | Oophorectomy |
| | Ovary | No/No | 43 | Oophorectomy, Chemo |

| | | | | |
|---|---|---|---|---|
| | Vagina | No/No | 73 | Rad |
| | Vagina | No/Yes | 66 | Chemo |
| | Vagina | Yes/Yes | 76 | Chemo |
| | Uterine cervix | No/No | NS | TAH |
| | Ovary | Yes/No | 25 | Oophorectomy, Chemo |
| | Ovaries | No/Yes | 13 | Oophorectomy, Chemo |
| | Ovary | No/Yes | 35 | Oophorectomy |
| [69] | Uterus | No/Yes | 73 | NS |
| [70] | Uterine cervix | No/No | 41 | Chemo |
| [71] | Uterine cervix | No/No | 49 | Rad, Chemo |
| [72] | Uterine cervix | Yes/No | 67 | Chemo |
| [73] | Ovary | No/No | 12 | NS |
| [74] | Ovary | No/No | 26 | Chemo |
| [75] | Uterine cervix | No/No | 48 | Chemo, hysterectomy, oophorectomy, AutoSCT |
| | Vagina | No/No | 48 | Chemo, hystectomy, surgery of proximal vagina, AutoSCT |
| [32] | Uterine cervix | Yes/No | 30 | Chemo |
| [34] | Ovary | No/Yes | 35 | Chemo |
| [76] | Uterine cervix | Yes/No | 30 | Chemo |
| [16] | Uterine cervix | No/No | 33 | Chemo |
| [77] | Ovary | No/Yes | 42 | Chemo |
| [78] | Uterus | Yes/Yes | 50 | Rad |
| [35] [a] | Uterine cervix | No/No | 37 | Chemo |
| | Uterine cervix | No/No | 34 | Chemo |
| | Uterus | No/No | 52 | NS |
| | Uterus, ovary | No/No | 35 | Chemo, AlloSCT |
| | Ovary | No/No | 25 | Chemo |
| | Ovary | No/Yes | 44 | NS |
| | Clitoris | Yes/No | 60 | Chemo |
| | Uterus, ovaries | No/No | 59 | Chemo |
| | Uterus | Yes/Yes | 46 | Chemo |
| | Uterine cervix | No/No | 43 | Chemo |
| | Uterus, ovary | No/No | 17 | Rad |
| [38] | Uterus | No/No | 49 | Chemo, AlloSCT |
| [79] | Uterus | No/Yes | NS | Chemo |
| [80] | Uterus | Yes/No | 49 | NS |
| [36] | Uterus | No/Yes | 50 | Chemo |
| [81] | Labia majora, vulva | No/Yes | 73 | Chemo |
| [82] | Uterus | No/Yes | NS | Chemo, TAH-BSO |
| [83] | Uterine cervix | No/Yes | 61 | Chemo |
| [84] | Uterus | No/Yes | 62 | Chemo |
| [85] | Vagina | No[c]/No | 52 | NS |
| [86] | Uterine cervix | No/No | 30 | Chemo, Rad |
| [30] | Uterus | Yes/No | 55 | Hysterectomy, Rad |
| [87] | Uterine cervix | Yes/No | 23 | Chemo |
| Present Case | Uterine cervix | Yes/Yes | 58 | Chemo, Rad, AlloSCT |

**Abbreviations:** AlloSCT: Allogeneic Stem Cell Transplantation; AutoSCT: Autologous Stem Cell Transplantation; BSO: Bilateral Salpingo-oophorectomy; Chemo: Chemotherapy; NS: Not Stated; Rad: Radiation; SO: Salpingo-oophorectomy; TAH: Total Abdominal Hysterectomy.

[a]Six patients underwent total abdominal hysterectomy (2 with bilateral and 2 with unilateral salpingo-oophorectomy), and 2 patients had oophorectomy; [b]Antecedents of chronic myeloid leukemia, granulocytic sarcoma of the female genital tract developed as manifestation of blastic transformation; [c] No antecedent of AML, but granulocytic sarcoma of the uterine cervix 11 years earlier.

uterus localization are mainly menometrorrhagia, or postcoital, or postmenopausal hemorrhage. The mass often extend to vagina and parametria, and even involved pelvic lymph nodes. Granulocytic sarcoma in the ovary tended to form large rather asymptomatic tumors. Localizations to the vulva and vagina often give physical findings suggesting Bartholin cysts. Granulocytic sarcomas have been rarely described as an initial presentation of AML and are mostly encountered in the course of AML as extramedullary relapse. It can precede or concur with bone marrow blastic infiltration. Diagnosis is often delayed, and prognosis almost always ominous evolving into refractory AML. Most patients who did not have manifest AML at presentation generally developed leukemia by few months. The average interval was estimated between 7.4 months [17] and 10.5 months [10]. A 67-month interval appears to be the longest interval reported [18]. Extramedullary AML appears more common in case of hyperleucocytosis, core binding factor (CBF) leukemia's, AML with a monocytic component, CD56 leukemia cell positivity and in long-term survivors (CBF leukemia's and patients allografted) in relationship with leukemia cell persistence in certain sites because of natural barriers or a specific microenvironment. It was also stated that the incidence of granulocytic sarcoma is twice as high in patients with chronic myeloid leukemia (CML) than in those with AML [10]. In the largest series of myeloid sarcomas, chromosomal aberrations were detected in 54% of cases [2]. Monosomy 7 (10.8%), trisomy 8 (10.4%) and *MLL*-spitting (8.5%) were the commonest abnormalities, whereas t (8; 21) was rare (2.2%). However, review of the literature highlights that such translocation has been detected in tumors occurring more often in childhood and/or at the orbital level [19,20].

The differential diagnosis involves mainly inflammatory lesions and a variety of malignant tumors, of which the most common incorrect diagnoses include malignant lymphoma, small cell carcinoma, sarcoma, and undifferentiated tumor. Leukemia cells generally do not disturb the natural architecture of the tissue, while there is tissue destruction and necrosis in lymphoma [21]. In granulocytic sarcoma, the borders of the nuclear outline of cells are irregular, the cytoplasm is eosinophilic, and eosinophilic myelocytes are predominant which could also be observed in T-cell lymphomas [22]. A number of antibodies react with myeloid cells and can be used for immunochemical analyses [23]. Most of the misdiagnoses were made on patients whose tumor preceded the overt leukemia [10]. Immunophenotyping appears then crucial for making the diagnosis. CD43 is expressed in most myeloid sarcomas. Granulocytic sarcomas also expressed CD13, CD33, CD117 and myeloperoxydase. Monocytic sarcomas are myeloperoxydase negative but express CD68, CD163 and lysozyme.

In the review of 89 cases from the literature (Table 1), the initial site of involvement was the uterine cervix in 37 cases (42%), the ovary in 22 cases (25%), and the vagina in 8 cases (9%). The other anatomic sites involved were uterus corpus (11 cases), labia majora (1 case), clitoris (1 case), and adnexal (1 case). In the other cases, the site of origin was not always precisely determined between uterus and ovary (3 cases), vulva and vagina (2 cases), uterine cervix and ovary (1 case), uterus and adnexal (1 case), and ovary and omentum (1 case). Median age at diagnosis was 42.5 years (range: 1 week – 76 years). Twenty cases of myeloid sarcoma of the gynecologic tract (22%) reported a prior history of myeloid neoplasm. In 33 cases (37%), there was a simultaneous bone marrow involvement by AML. In 43 cases (48%), the female genital tract was the only site of disease at the time of presentation without any known history of hematologic malignancy. When the uterus is involved, the disease is usually limited to the cervix. Involvement of uterine body is uncommon. As it was the case in our patient, these tumors can be locally invasive and can cause ureteric obstruction. Granucytic sarcoma of the genital tract appeared more frequent in women than in men [8]. There is no clear explanation for this male/female discrepancy. However, several publications have reported concomittant granulocytic sarcoma of the female gynecologic tract and granulocytic sarcoma in breasts [24-27]. It has then been postulated that some AML may have steroid hormonal receptors [27], which was not confirmed further. The type of AML was not always indicated. However, several cases reported CBF leukaemia's [16,28-36]. The mechanism of the occurrence of granulocytic sarcoma may be related to the deregulation of CBF transcription factors involved in cell recognition and adhesion. This type of leukemia has also been reported to form solid tumors in the central nervous system [37]. Despite an overall favourable prognosis of CBF leukemia subtype when treated with intensive chemotherapy including high-dose cytarabine, it remains uncertain what constitutes the best treatment in this specific situation. High-dose chemotherapy and stem cell transplantation may benefit for these patients [31]. Similarly, monoblastic sarcomas with 11q23/*MLL* rearrangements have often been observed [38]. This supports a therapy-related origin of the myeloid sarcoma. Leukaemia's with *MLL* gene rearrangement have been reported after chemotherapies that include topoisomerase II inhibitors [39]. In our case report, *MLL* gene rearrangement was identified at the time of relapse, while it was not present at the time of initial diagnosis.

Our observation suggests that despite evidence of localized disease, myeloid sarcoma is indicative of widespread systemic disease and should be treated accordingly. Treatment should be centred on the underlying leukemia. Treatment of uterine myeloid sarcoma has been described with combinations of surgery, radiation and chemotherapy. In the current case, surgery was avoided because of the wide tumor involvement. It has been shown that patients with no discernible hematologic abnormality at diagnosis who received no chemotherapy developed AML in more than 80% of cases within 11 months [10,29]. Reversely, it was demonstrated that almost half of the patients who received chemotherapy remained in a non-leukemic stage for a long period of time [29,40]. Therefore, cases presenting as isolated myeloid sarcoma should receive similar therapy as for AML with the same cytogenetic abnormality. Granulocytic sarcoma responds well to radiotherapy, but it is unclear whether radiotherapy improves survival [41]. The role of local therapy such as radiation remains unknown. Irradiation therapy did not seem to improve

the disease free interval and the prognosis, but could be discussed in case of residual sites of malignant activity after chemotherapy. Granulocytic sarcoma of the female genital tract appears to have a prognosis similar to that of granulocytic sarcomas at other body sites. Surgical resection of the bulk of the tumor has only a diagnostic interest, but because of obvious residual disease, patients should receive adjuvant chemotherapy. Extramedullary disease is often considered as an adverse prognostic factor in AML [2]. Although the occurrence of a granulocytic sarcoma in a patient with AML does not seem to alter the prognosis [10] most if not all long survivors received stem cell transplantation. Myeloid sarcoma would therefore represent an indication of treatment by allogeneic hematopoietic stem cell transplantation.

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