Multiple Isolated Extramedullary Relapse and Long-term Survival of One AML Patient

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Case Report

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Abstract

**Background:** Granulocytic sarcomas (GS) are very rare. If it occurs after complete remission of acute myeloblastic leukemia (AML), it indicates a recurrence of AML and a poor prognosis. In such cases, relapse of leukemia occurs within a mean of 10 months following granulocytic sarcoma.

**Case presentation:** Here we present an unusual case of a 78-year-old male who presented with AML-M1 38 years ago. After complete remission from AML-M1 6 years later, he developed unusual multiple isolated extramedullary relapses. And the extramedullary relapse occurred 7 times and involved 8 anatomic sites during 15 years. Despite repeated relapses, treatment and physical damage, the patient managed to survive into 2016. However, we did not detect any signs of leukemia after 1992 and his bone marrow and peripheral blood remained normal until his death. Immunohistochemical results of our case are all the same, suggesting that they were all derived from the recurrence of the same tumor.

**Conclusions:** Extramedullary relapses may occur in AML patients after complete relieve and without the blood count and BM involvement. Accurate diagnosis of GS is important so the patient could be treated timely. It is a challenge for the pathologist to make the diagnosis, and without immunohistochemistry (IHC), it may be misdiagnosed as another tumor.

**Background**

Granulocytic sarcoma, as known as chloroma, myeloblastoma or extramedullary myeloid cell tumor, is a localized extramedullary tumor composed of one or more of the myeloid lineages [1,2]. It usually presents as a nodular mass in the course of acute myeloid leukemia or associated with various myeloproliferative diseases, occurring in any age and affecting all parts of the body. Rarely, the tumor can develop in a patient after complete remission from the acute myeloid leukemia [1] and it suggests the recurrence of leukemia and the poor prognosis. Here we present an unusual case, the patient developed granulocytic sarcoma seven times after longstanding complete remission from AML-M1 without BM and peripheral blood involvement. Curiously, the patient remained normal of blood count and BM for 34 years until he died.

**Clinical history**

In May 1988, a 40-years-old man found two masses in the left popliteal fossa and right maxillary sinus. Mass at popliteal fossa was partially resected and postoperative pathological diagnosis was synovial sarcoma. The patient received chemotherapy and radiotherapy and then the mass in the right maxillary sinus was disappeared and the clinical symptom was completely relieved.

In October 1992, two masses were found in left epididymis near the sperm duct and spermatic vein, respectively. The surgically excised tissues were sent to the pathology department. We reviewed the previous hematoxylin-eosin (HE) section and inquired about the patient's detailed medical history. Unexpectedly, we learned the history that the patient had got acute myelogenous leukemia (AML-M1) in 1982. Therefore, chloroacetate esterase (CAE) histochemical staining was performed and supported the diagnosis of granulocytic sarcoma. Combining morphological features with a detailed history and CAE staining results, we rendered a diagnosis of granulocytic sarcoma. The previous diagnosis of popliteal fossa biopsy was also revised as granulocytic sarcoma. However, hemogram and myelogram were normal all the time. The patient received chemotherapy and discharged.

Another subcutaneous mass was found in the right forearm in November, 1997. The mass was removed by surgery, and pathological diagnosis from outside the hospital was lipobroma with chronic inflammation. Another local mass was noted shortly after the operation. The tumor grew to the fist-size after 6 months, so the patient was admitted to our hospital again, and the clinical suspected that it was granulocytic sarcoma, not fibrosarcoma. The patient was given surgical resection in July 1998. The pathological diagnosis was granulocytic sarcoma. BM aspiration showed no evidence of systemic relapse. After treatment, the patient achieved complete remission and discharged from our hospital.

From August 1998 to April 2003, the patient had occurred extramedullary relapse four times. The details were shown in table 1 and H&E stain shown in Fig 1. The blood count and BM were always normal. After 2003, he did not develop granulocytic sarcoma or leukemia again until his death in October 2016. The timeline of his illness is clearly shown in Fig 2.

**Pathologic finding**

All of the dissected tissues were given retrospective HE staining and immunohistochemical staining. The microscopic histologic findings were roughly the same: tumor cells were proliferated diffusely in the popliteal fossa, subcutaneous adipose tissue of the forearm, the area between skeletal muscles, the area below nasal mucosa epithelium and area between seminiferous tubules. While focal aggregation and
infiltration of the tumor cells were found in epididymal mesenchyme. The tumor cells also invaded into the surrounding soft tissue. Some tumor cells were arranged in “Indian file”. The tumor cells were of medium size and relatively consistent shape. The cytoplasm was little and lightly dyed, while the nuclei were in round or ovoid. Nuclear chromatin was fine and distributed uniformly. 1 or 2 small basophilic nucleoli can be seen. Mitosis was common, with 1~2/HPF. Immature eosinophil was not seen. It was blast type granulocytic sarcoma based on the histological classification. A panel of antibody including MPO, CD34, CD117, CD43, CD15, CD68, PG-M1, CD68, KP1, CD56, LCA, CD99, CD3, CD20, and Ki-67 were used to make immunohistochemical staining by streptavidin-perosidase method. The results of immunohistochemistry stains showed in Table 1. Immunohistochemical results of our case are all the same, suggesting that they were all derived from the recurrence of the same tumor.

Discussion

GS is a localized extramedullary tumor composed of immature myeloid cells. The common sites of involvement are the bone, orbit, peristome, soft tissue, lymph nodes, and skin [1]. MS may be the first manifestation of AML, precede it by months or years, or equally represent the initial manifestation of relapse in a previously treated AML in remission. Aleukemic granulocytic sarcoma is very rare. It usually means systemic relapse and poor prognosis. In such case, relapse of leukemia occurs within an average of 10 months following MS and the prognosis is usually poor [3]. Our case is different from cases previously reported and its uniqueness is in that:

1. The patient had 7 times of extramedullary granulocytic sarcomas after acute myelogenous leukemia, involving 8 different anatomical sites, which is to our knowledge for the first time. After all, isolated extramedullary relapse is really rare. Byrd et al. reported a case with AML in remission who had a series of 11 granulocytic sarcomas appearing periodically over a 29-interval without evidence of BM recurrence [4]. Somjee et al. reported a 5-year old patient with AML-M2, who had myeloid sarcoma in 7 different anatomical parts of the body at the same time [5]. Jung and colleagues reported a patient with AML who had been in CR for 9 years, developed myeloid sarcoma in the form of multiple intrathecal masses and no systemic signs of AML had been observed for seventeen months of the follow-up [6]. As to the mechanism of granulocyte sarcomas in extramedullary development, we think that it may be homing phenomenon with tumor cells, similar to the homing of T cells into the skin via interaction with integrins and endothelial-bound chemokines, which suggested as a mechanism of extramedullary invasion of leukemic cells [7]. MS might be an aberrant homing signal for the leukemic blasts precluding the more common BM localization. This may represent a subclone of the whole original AML clone in cases of concurrent presentation or in the relapse situation [1]. It is also worth considering whether this homing phenomenon is related to the recurrence site.

2. The patient survived for 34 years after AML, in spite of AML is a malignant hematopoietic tumor with a poor prognosis. To the best of our knowledge, he is the patient with acute myeloid leukemia who has the longest survival time so far reported. Akinori Wada [8] reported a case who had a relapse of acute myeloid leukemia after allogeneic cell transplantation in the long-term survival of more than 10 years. Niccolò Bolli reported a case with occurred myeloid sarcoma 20 years after the initial diagnosis of acute myeloid leukemia [9]. We are curious about why the patient has such a long-term survival. The patient's individual differences must be one of the reasons. However, effective treatment and high treatment response every time, are equally important and worth thinking about.

3. After the first complete remission of AML, the blood count and bone marrow of the patient remained completely normal despite the relapse of granulocyte sarcomas 7 times during the disease, which was very surprising, and the patient did not show any signs of leukemia until the final death.

For rendering a diagnosis of granulocytic sarcoma, the histopathologic examination is necessary. Combining a panel of IHC staining with a detailed history, is helpful in differential diagnosis with lymphoma, PNET/Ewings sarcoma and other small cell neoplasms. The tumor cells can express MPO, CD43, lysozyme, CD68 (KP1), CD99, CD117 and LCA. The absence of clinical history and IHC staining results will lead to misdiagnosis, as was the initial diagnosis in this case. We should be aware that multiple isolated extramedullary relapses may occur in patients with leukemia, even if the patient got a complete relieve and the blood count and BM were normal after the treatment. Therefore, long-term follow-up and regular physical examination are necessary. Clinicians and pathologists need to be especially aware of the clinical symptom appearance of granulocyte sarcoma.

Abbreviations

GS: Granulocytic sarcomas; AML acute myeloblastic leukemia;

CAE: chloro-acetate esterase; IHC: immunohistochemistry; HE: hematoxylin-eosin

Declarations
Ethics approval and consent to participate

Written informed consent was obtained from the patient.

Consent for publication

Not applicable.

Availability of data and material:

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Weiping Liu made the pathological diagnosis of the patient. Yang Liu and Yunzhu Li analyzed the data. The immunohistochemical results. Jiman Li did the follow-up and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Clinical pathologic features of the relapsed myeloid sarcomas
| NO. | Time      | Sites                      | Quantity | Size                        | Treatment                                                                 | Peripheral blood | Bone marrow |
|-----|------------|----------------------------|----------|-----------------------------|---------------------------------------------------------------------------|------------------|-------------|
| 1   | May. 1988  | Left popliteal fossa       | 1        | 4.5cm×3cm×1.5cm             | D Co$^{60}$6800cGy Vincristine, cyclophosphamide and actinomycin D for 1 cycle, vincristine for 1 cycle, cyclophosphamide, Adriamycin and dacarbazine citrate for 4 cycles | N                | N           |
|     |            | Right maxillary sinus      | 1        | NC                          | ND Co$^{60}$6046cGy                                                      |                  |             |
| 2   | Oct. 1992  | Left epididymis            | 2        | 3cm×1.5cm×1cm and 2cm×2cm×2cm | D ND Etoposide, cytarabine and rubidomycin for 6 cycles                   | N                | N           |
| 3   | Nov. 1997  | Left forearm               | 1        | diameter of about 2cm       | D Co$^{60}$3966 cGy Mitoxantrone and cytarabine for 6 cycles (Aug. 1998)   | N                | N           |
|     | July 1998  |                            | 1        | 4cm×3cm×3cm                 | D (Aug. 1998)                                                            |                  |             |
| 4   | Aug. 1998  | Right nasal cavity         | 1        | diameter of about 1cm       | Biopsy Co$^{60}$3999 cGy                                                | N                | N           |
| 5   | Mar. 2000  | Left waist                 | 1        | 1cm×1cm×1cm                 | D Co$^{60}$3000 cGy                                                      | N                | N           |
| 6   | Oct. 2001  | Left thigh                 | 1        | diameter of about 2cm       | ND Co$^{60}$3000 cGy Homoharringtonine and cytarabine for 1 cycle, daunorubicin and cytarabine for 2 cycles | N                | N           |
| 7   | Apr. 2003  | Right testicle             | 1        | 5cm×4cm×3.5cm               | D ND Daunorubicin and cytarabine for 3 cycles                            | N                | N           |

NC=not clear; ND=not done; N=normal; D=done.

Table 2 Immunophenotypic features of the relapsed myeloid sarcomas

| Sites                        | MPO | CD34 | CD117 | CD43 | CD15 | CD68 [PG-M1] | CD68 [KP1] | CD56 | LCA | CD99 | CD3 | CD20 | Ki67 |
|------------------------------|-----|------|-------|------|------|--------------|------------|------|-----|------|-----|------|------|
| Left popliteal fossa         | +   | -    | +     | +    | -    | -            | +          | -    | +   | -    | -   | -    | 60%  |
| Left epididymis              | +   | -    | +     | +    | -    | -            | +          | -    | -   | +    | -   | -    | 50%  |
| Left forearm                 | +   | -    | +     | +    | -    | -            | +          | -    | +   | -    | -   | -    | 60%  |
| Right nasal cavity          | +   | -    | +     | +    | -    | -            | +          | -    | +   | -    | -   | -    | 60%  |
| Left waist                  | +   | -    | +     | +    | -    | -            | +          | -    | +   | -    | -   | -    | 60%  |
| Right testicle              | +   | -    | +     | +    | -    | -            | +          | -    | +   | -    | -   | -    | 60%  |

Figures
Figure 1

A: Popliteal fossa: blast cells invading fibrous tissue, with round nuclei and scant cytoplasm, HE×400
B: Epididymis: focal invasion of tumor cells into epididymal mesenchyme, HE×400
C: Subcutaneous tissue of left forearm: blast cells invading fibromuscular stroma, HE×400
D: Right nasal cavity: abundant infiltration of small, monomorphic and discrete tumor cells with a small amount of blood vessel mesenchyme, HE×400
E: Left waist: blast cells invading fibrous tissue, HE×400
F: Testicle: blast cells diffuse infiltrating testicle tissues with residual seminiferous tubule, HE×400

Figure 2

The illness timeline of patient