Vulvar myeloid sarcoma as the presenting symptom of acute myeloid leukemia: a case report and literature review of Chinese patients, 1999–2018

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Abstract

Background: Myeloid sarcoma (MS), which represents a rare malignancy that comprises of myeloid blasts occurring at extra-medullary sites, closely correlates with the onset and relapse of acute myeloid leukemia (AML) and other hemopoietic neoplasm. Female genital system is an uncommon location of MS, with the vulvar MS being even rarer that only eight cases have been reported in English-written literature.

Case presentation: A 47-year-old woman presented with chronic ulceration on her vulva for one and a half month. Microscopic examination of incisional biopsy revealed dermal infiltration of myeloid precursor cells, which were positive for MPO, lysozyme, CD43, CD68, CD38 and CD117. Bone marrow flowcytometric analysis showed myeloblast count of 74%, which expressed CD13, CD33, CD117 and HLA-DR. A diagnosis of AML (M2 type) was made and vulvar MS was the earliest symptom. The patient achieved complete remission after chemotherapy with no evidence of recurrence in a 27-month follow-up. We reviewed the literature and identified 54 cases of Chinese patients with gynecological MS between 1999 and 2018, and discovered that in Chinese population, MS most frequently involved uterine cervix followed by the ovary and vulva, and ovarian MS onset much earlier than other sites. Remarkably, vulvar MS exhibited a high rate of concurrent AML and secondary myeloid leukemia within a short time of its occurrence. Despite its limited distribution, MS should be tackled aggressively with chemotherapy followed by allogeneic hematopoietic stem cell transplantation if the appropriate donor is available.

Conclusions: Female genital MS, especially vulvar MS, should be included in the differential diagnosis of gynecological neoplasm, which will facilitate its early diagnosis and prompt management.

Keywords: Myeloid sarcoma, Acute myeloid leukemia, Female genitalia, Vulva, Chemotherapy

Background

Myeloid sarcoma (MS) represents a rare malignancy that encompasses immature or mature myeloid blasts occurring at any extra-medullary site with normal architectural effacement. It was first described by Burns [1] in 1811 and termed as chloroma by King [2] in 1853 because a subset of MS contains abundant myeloperoxidase (MPO) and turns green upon exposure to oxygen [3, 4]. Dock identified the association of MS with acute leukemia in 1893 [5], and Rappaport referred it as “granulocytic sarcoma” in 1996 for the neoplasm comprises of immature granulocytic cells and resembles a sarcoma [6]. Although other historical names have been used, MS was recommended by world health organization in 2001. MS might be isolated [7, 8], precede [9], coincide with the onset [10] and relapse [11] of AML, as well as correlated with myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) [12]. The incidence of MS is between 1.1 and 9.1% in patients with AML, MDS or MPN [11, 13]. MS occurs in nearly any sites, and the most common sites include lymphoid tissues, central...
nervous system, lung, kidney and gastrointestinal tract [14]. Female genital system is a much rarer location that less than a hundred cases have been reported in English-written literature [8, 10, 11]. The frequency of gynecological involvement from high to low was the ovary, cervix, uterus and vulva [10, 15]. Precisely, only 8 MS patients involving the vulva were identified in literature [16]. Here, we report an unusual case of vulvar MS as the initial presentation of AML, and review the literature of Chinese patients with gynecological MS.

Case presentation
A 47-year-old woman presented with fever and chronic ulceration on her vulva for one and a half month in January 2017. The patient had no significant past medical or family history. She had been given levofloxacin and topical douche in another hospital, but the vulvar lesions continued to aggravate. Gynecological evaluation revealed two large well-demarcated ulcers on bilateral labia majora (Fig. 1) without involvement of labia minora and vagina. The patient underwent an incisional biopsy and the cut surface of specimen was grey-white. Microscopically, the dermis was infiltrated with diffuse noncohesive sheets of medium-sized myeloid precursor cells that have large vesicular nuclei, prominent nucleoli, and scarce ill-defined cytoplasm with mild pleomorphism (Fig. 2a). Abundant neutrophils and sparse plasma cells were observed. Immunohistochemistry (IHC) demonstrated positive reactions with MPO (Fig. 2b), lysozyme (Fig. 2c), CD43 (Fig. 2d), CD68 (Fig. 2e), CD38 and CD117, and negative reactions with T-cell markers (CD3, CD5, CD56), B-cell markers (CD20, Bcl-2, Bcl-6) and plasma-cell makers (CD138). Ki-67 was expressed in 80% of the neoplastic cells (Fig. 2f). Therefore, she was diagnosed as MS and admitted to hospital.

On admission, her peripheral blood count showed white blood cells $6.78 \times 10^9/L$, hemoglobin 80 g/L, hematocrit 26%, platelets $6.78 \times 10^9/L$. Differential blood count was as follows: blasts 71%, unclassifiable cells 16%, neutrophils 24%, lymphocytes 58%, monocytes 2%. Her peripheral blood smear revealed the percentage of leukemic cells was 28%, while the bone marrow (BM) aspirate contained 44.5% leukemic cells. Flowcytometric analysis showed myeloblast count of 74%, which expressed CD13, CD33, CD117 and HLA-DR. Cytogenetic study of the BM discovered a normal 46, XX karyotype. Fluorescence in situ hybridization (FISH) analysis did not detect any common fusion genes in hematologic diseases such as AML, MDS, eosinophilia and acute lymphoblastic leukemia (ALL). Given the results, a diagnosis of AML (M2 type, FAB classification) was made and MS of the vulva was the earliest symptom in this patient.

She subsequently received induction chemotherapy with idarubicin (10 mg/m² for 3 days) and cytarabine (100 mg/m² for 7 days) that achieved complete remission 1 month later with the ratio of minimal residual disease being 0.017%. Meanwhile, the vulvar ulceration healed without other therapy (Fig. 3). In this period, the patient developed upper gastrointestinal bleeding and acute

![Fig. 1 Two large well-demarcated ulcers on bilateral labia majora](image1)

![Fig. 2 Hematoxylin-eosin and immunohistochemical staining of vulvar ulcers. Diffuse noncohesive sheets of medium-sized myeloid precursor cells in the dermis (a); Immunohistochemical staining result is positive for myeloperoxidase (b), lysozyme (c), CD43 (d), CD68 (e) and ki-67 (f).](image2)
inferior myocardial infarction that recovered after conservative treatment. She then received 5 cycles of intensification therapy (high-dose cytarabine 3 g/m²/12 h for 3 days) along with intrathecal injection of methotrexate and cytarabine for 4 times. Neither a family nor unrelated donor for haematopoietic stem cell transplantation (HSCT) had been found. Currently, she remained in complete remission 27 months from the time of diagnosis on follow up.

Discussion and conclusions

We searched following terms of “genitals and MS” and “genitals and AML” in the PubMed and Chinese literature databases including Wanfang Data (http://www.wanfangdata.com.cn/index.html), VIP Journals (http://qikan.cqvip.com/) and China Knowledge Resource Integrated Database (http://www.cnki.net/). In total, we identified 54 MS cases involving gynecologic tract reported between 1999 and 2018, details of which are summarized in Table 1.

Being a rare entity, isolated MS often poses diagnostic challenge, and immunohistochemical examination is of great importance in the correct diagnosis. As the myeloblasts in MS have an antigen profile resembling that of the blasts and precursor cells in AML, the positivity of myeloperoxidase, CD43, CD68, CD117 and lysozyme help to recognize MS. The most important differential diagnoses include non-Hodgkin lymphoma of the lymphoblastic type, Burkitt’s lymphoma, large-cell lymphoma and small round cell tumors [61]. However, we did not detect any exclusive surface marker of MS involving gynecological tissue.

Our reviewed cohort showed that gynecological MS involved uterine cervix (40%), ovary (23.6%), vulva (10.9%), uterine body (5.5%) and vagina (3.6%) in a most-preferred-to-least-preferred order with around one sixth of cases had multifocal lesions, which differed from previous notion that the most frequently involved genital organ is the ovary followed by the cervix and uterus [10, 15, 62]. The inconsistency might partly result from ethnic diversity. A ‘skip’ phenomenon was also noticed in nearly half of the multifocal MS patients that the myeloblasts occurred at non-adjacent sites, which is uncommon in other gynecological malignancy.

The age of female-genital MS onset ranged from 22 to 78 years with an average age being 39.2 ± 1.7 years (Table 2), which differed from a predilection of general MS for children [63]. Particularly, MS arising at the ovaries mostly occurred in young adults, which was much earlier than the other single locations (27.5 ± 1.4 vs 43.5 ± 2.3, P = 0.0001). Female-genital MS could be asymptomatic (6 cases) or initially presented as mass formation (9 cases), abdominal pain (8 cases), ulceration (1 case), paramenia and vaginal bleeding (25 cases), which was similar to an earlier observation [64]. Remarkably, the onset symptom of all the previously-reported vulvar MS was regional mass with our case distinctively being ulceration.

Three fifths of MS patients are not correlated with AML or other hematopoietic disorders, with equally 14.9% cases preceding or coinciding with AML and 10.6% occurring as the first sign of AML relapse (Table 2). While the few cases of vagina and uterine-body MS revealed no linkage with AML, vulvar MS exhibited a notably high rate of concurrent AML and secondary myeloid leukemia in a short time. The interval between the initial diagnosis of MS and systemic disease with medullary involvement ranged from 0.6 to 18 months with a mean value of 5.5 month, in accordance with the formerly-reported 5 to 11 months [65–67]. And, MS heralded AML relapse with or without marrow involvement, and the duration was from 6 to 67 months with a mean value of 33.6 months.

As evidenced from prior observation, FAB subtype M4 and M5 are mostly associated with extra medullary tissue involvement [16]. Unexpectedly, our reviewed cohort displayed a predominance of M2 subtype (10 cases) with the remaining being M5 (2 cases) and M3 (1 case), suggesting that M2 subtype of AML was most inclined to develop MS in the Chinese population. The chromosomal abnormalities of MS include trisomy 4, trisomy 8,
## Table 1: Reviews of Chinese cases of gynecological myeloid sarcoma

| No. | Author            | Age | Time of genital involvement | Non-systemic involvement | Systemic involvement | AML Type | Treatment                                 | Outcome                          |
|-----|-------------------|-----|-----------------------------|--------------------------|----------------------|----------|-------------------------------------------|----------------------------------|
|     |                   |     |                             |                          |                      |          |                                           |                                  |
|     |                   |     |                             |                          |                      |          | CR, ANEL 36 mo                           |                                  |
|     |                   |     |                             |                          |                      |          | CR, died 3 mo (sepsis)                    |                                  |
|     |                   |     |                             |                          |                      |          | CR, ANEL 27 mo                           |                                  |
|     |                   |     |                             |                          |                      |          | Died 10 mo                               |                                  |
|     |                   |     |                             |                          |                      |          | Died 2 mo (cerebral hemorrhage)          |                                  |
|     |                   |     |                             |                          |                      |          | Died 3 mo                                |                                  |
|     |                   |     |                             |                          |                      |          | Died 2 mo                                |                                  |
|     |                   |     |                             |                          |                      |          | Died 2 mo                                |                                  |
|     |                   |     |                             |                          |                      |          | Died 12 mo                               |                                  |
|     |                   |     |                             |                          |                      |          | Alive 91 mo                              |                                  |
|     |                   |     |                             |                          |                      |          | Died 6 mo                                |                                  |
|     |                   |     |                             |                          |                      |          | Died 20 mo                               |                                  |
Table 1  | Reviews of Chinese cases of gynecological myeloid sarcoma (Continued)

| No | Author | Age | Time of genital involvement | Non-systemic involvement | Systemic involvement | AML Type | Treatment | Outcome |
|----|--------|-----|-----------------------------|--------------------------|----------------------|----------|-----------|---------|
|   |        |     |                             |                           |                      |          |           |         |
|   |        |     |                             |                           |                      |          |           |         |
|   |        |     |                             |                           |                      |          |           |         |
| 31 | Wang et al. [42] | 38 | Isolated | None | None | NA | SG | Not stated |
| 32 | Zhao et al. [43] | 33 | Isolated | None | None | NA | CT (DNR + ARA-C) | Alive |
| 33 | Hou et al. [44] | 44 | Isolated | None | None | NA | Not stated | Not stated |
|   |        |     |                             |                           |                      |          |           |         |
| 34 | Zhang et al. [45] | 27 | Initial | None | Simultaneously | M2 | CT (DNR + ARA-C) | PR, MS resolved |
| 35 | Zheng et al. [46] | 26 | Isolated | None | None | NA | SG → CT (DNR + ARA-C) → Auto-HSCT | ANEL 1 y after HSCT |
| 36 | Yu et al. [47] | 26 | Relapse (AML) | None | None | NA | SG | Not stated |
| 37 | Yu et al. [47] | 35 | Isolated | None | None | NA | SG | Not stated |
| 38 | Zhou et al. [48] | 27 | Initial | None | After 2 mo of MS | M2 | SG → CT (DNR + ARA-C) | Not stated |
| 39 | Zhou et al. [49] | 26 | Relapse (AML-M2) | None | None | NA | SG | Not stated |
| 40 | Zhou et al. [50] | 23 | Isolated | None | None | NA | SG → CT (DNR + ARA-C) | Not stated |
| 41 | Zhu et al. [51] | 22 | Relapse (AML-M3) | None | None | NA | SG → CT | Died 39 mo |
| 42 | Zhu et al. [52] | 27 | Initial | None | Simultaneously | M2 | SG → CT (DNR + ARA-C) | Died 1 mo (cerebral hemorrhage) |
| 43 | Zhang et al. [53] | 29 | Initial (vulva, ovary) | Whole body | Not stated | NA | Refused | Died 1 mo |
| 44 | Cheng et al. [54] | 22 | Relapse (AML-M3) | None | None | NA | CT (VP-16 + ARA-C) | Died 1 mo |
| 45 | Qu et al. [55] | 44 | Relapse (AML-M2a) | None | None | NA | SG → CT | ANEL 1 y |
| 46 | Li et al. [56] | 25 | Uterine cervix, vagina | Lymphadenopathy | Not stated | NA | CT (PTX + PDD) → RT + CT (DNR + ARA-C) | MS resolved, ANEL 6 mo after cessation of CT |
| 47 | Wu et al. [57] | 43 | Uterine cervix, vagina | None | None | NA | CT (IDA + ARA-C) | CR, ANEL 3 mo |
| 48 | Wang et al. [58] | 46 | Relapse (AML-M2) | None | None | NA | CT (DNR + ARA-C, DNR + ARA-C, DNR + ARA-C, DNR + ARA-C) | Cervical M5 resolved, ANEL 7 mo |
| 49 | Long et al. [59] | 43 | Uterine cervix, vagina | None | None | NA | CT (MTX + ARA-C, MTX + ARA-C, MTX + ARA-C, MTX + ARA-C) | ANEL 8 mo |
| 50 | Huang et al. [60] | 51 | Uterine cervix, | Colon, rectum | Not stated | NA | CT | Died 11 mo |

ADM: Adriamycin, AML: acute myeloid leukemia, ANEL: alive with no evidence of leukemia, ARA-C: cytarabine, CR: complete remission, CT: chemotherapy, CTX: Cyclophosphamide, d: day, DNR: daunorubicin, FA: Fluorouracil, HHT: homoharringtonine, HSCT: hematopoietic stem cell transplantation, Allo-HSCT: allogeneic HSCT, Auto-HSCT: autologous HSCT, IDA: idarubicin, IL: intrathecal injection, LA: lymphadenopathy, MIT: Mitoxantrone, MDS: myelodysplastic syndrome, mo: month, NA: not applicable, PED: Prednisone, PDD: cisplatin, PR: partial remission, PTX: paclitaxel, RT: radiotherapy, SCC: squamous cell carcinoma, SG: surgery, TCL: T cell lymphoma, VCR: vincristine, VP-16: etoposide, y: year.
trisomy 11, monosomy 7, 16(q)-, 5q- and 20q-, while t (8;21)(q22;q22) and inv [16] (p13q22) were the most common chromosome rearrangements detected in AML-correlated MS [12, 68]. In our reviewed cases, three occurred t (8;21)(q22;q22), in conformity with the high incidence of t (8;21) in AML-M2 patients with MS [68]. And, one AML-M5 patient had complex chromosomal aberrations of t (1;7)(p22;q36), t (3;21)(q22;q26) and loss of chromosome 16 [20]. Recurrent AML1/ETO fusion genes were identified in two gynecological MS patients, whereas no cytogenetic defect was discovered in five patients.

Despite the local distribution of MS, chemotherapy was more effective than radiation MS and reviewed Chinese MS cases specifically involving gynecological MS. We discovered that MS most frequently involved uterine cervix followed by the ovary and vulva, and ovarian MS onset much earlier than other sites. Moreover, vulvar MS exhibited a notably high rate of concurrent AML and secondary myeloid leukemia in a short time, which require immediate management. Despite its limited distribution, MS should be tackled aggressively with chemotherapy followed by allogeneic HSCT if the appropriate donor is available. Female genital MS, especially vulvar MS, should be included in the differential diagnosis of gynecological neoplasm, which will facilitate its early diagnosis and prompt management.

In summary, we herein reported a rare case of vulvar MS and reviewed Chinese MS cases specifically involving gynecological system. We discovered that MS most frequently involved uterine cervix followed by the ovary and vulva, and ovarian MS onset much earlier than other sites. Moreover, vulvar MS exhibited a notably high rate of concurrent AML and secondary myeloid leukemia in a short time, which require immediate management. Despite its limited distribution, MS should be tackled aggressively with chemotherapy followed by allogeneic HSCT if the appropriate donor is available. Female genital MS, especially vulvar MS, should be included in the differential diagnosis of gynecological neoplasm, which will facilitate its early diagnosis and prompt management.

**Abbreviations**

- AML: Acute myeloid leukemia
- ANEL: Alive with no evidence of leukemia
- ARA-C: Cytarabine
- Auto-HSCT: Autologous HSCT
- BM: Bone marrow
- CR: Complete remission
- CT: Chemotherapy
- CTX: Cyclophosphamide
- DNR: Daunorubicin
- FA: Fludarabine
- FISH: Fluorescence in situ hybridization
- HHT: Homoharringtonine
- HSCT: Hematopoietic stem cell transplantation
- IDA: Idarubicin
- IHC: Immunohistochemistry
- II: Intrathecal injection
- LA: Lymphadenopathy
- MDS: Myelodysplastic syndrome
- MPO: Myeloperoxidase
- MPN: Myeloproliferative neoplasm
- Mo: Month
- MPO: Myeloperoxidase
- NA: Not applicable
- PDD: Cisplatin
- PED: Prednisone
- PR: Partial remission

**Table 2** Onset age and correlation with AML of reviewed myeloid sarcoma patients

| MS site      | Onset Age (year) | Without AML | Preceding AML | Coinciding with AML | AML Relapse |
|--------------|------------------|-------------|---------------|---------------------|-------------|
| Vulva        | 25–78 (49.5 ± 9.3)| 1 (16.7%)   | 1 (16.7%)     | 4 (66.7%)           | —           |
| Vagina       | 55–61 (58 ± 3)   | 1 (100%)    | —             | —                   | —           |
| Uterine cervix| 23–63 (41 ± 2.2)| 10 (58.8%)  | 4 (23.5%)     | 2 (11.8%)           | 1 (5.9%)    |
| Uterine body | 33–44 (38.3 ± 3.2)| 3 (100%)    | —             | —                   | —           |
| Ovary        | 22–36 (27.5 ± 1.4)| 8 (66.7%)   | 1 (8.3%)      | 1 (8.3%)            | 2 (16.7%)   |
| Multifocal   | 25–51 (40.1 ± 2.8)| 5 (62.5%)   | 1 (12.5%)     | —                   | 2 (25%)     |
| Total        | 22–78 (39.2 ± 1.7)| 28 (59.6%)  | 7 (14.9%)     | 7 (14.9%)           | 5 (10.6%)   |

**AML acute myeloid leukemia**
The ethical approval and documentation for a case report was waived with the consent of the patient's lesion, and collected literature. PH and XZ analyzed patient data and wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Please contact author for data requests.

Ethics approval and consent to participate
The ethical approval and documentation for a case report was waived with the consent of the patient's lesion. PH and XZ collected literature. PH and XZ analyzed patient data and wrote the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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