Lymph node myeloid sarcoma with TP53-associated myelodysplastic syndrome: A case report

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Abstract. Myeloid sarcoma (MS) is a rare extramedullary tumor mass that carries a high risk of progression to acute myeloid leukemia (AML), and patients with MS are commonly treated with the AML regimen. However, MS is frequently misdiagnosed due to its lack of clinical specificity. Patients with MS who harbor tumor protein p53 (TP53) mutations and complex karyotypes are considered to have a poorer prognosis. The present study reports a case of lymph node MS with TP53 (V173G)-related myelodysplastic syndrome (MDS). The mass was first considered to be a lymphoma and treated as such. However, following immunohistochemical analysis, which revealed cells positive for CD43, myeloperoxidase and CD117, the patient was later diagnosed with MS combined with MDS. The patient went into complete remission after the first cycle of chemotherapy, and showed a decrease in platelet, red blood cell and white blood cell counts following the second cycle of chemotherapy. After the third chemotherapy, agranulocytosis occurred, leading to refractory pneumonia and eventually death due to respiratory failure. MS with TP53-related MDS has a low incidence rate, a poor prognosis and a short survival time. The clinical manifestations of MS are non-specific and easy to misdiagnose, leading to delayed diagnosis and treatment, and ultimately worsening the prognosis of the patients. Therefore, a lymph node biopsy should be performed as soon as possible for patients with lymph node enlargement, and early treatment should be carried out to prolong the survival period.

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Introduction

Myeloid sarcoma (MS) is a rare extramedullary tumor mass composed of primitive or immature myeloid cells of myeloid origin, and is also known as a green tumor or granulocytic sarcoma. MS is classified as a type of acute myeloid leukemia (AML) by the World Health Organization (1). The tumor can manifest as primary bone marrow sarcoma with or without bone marrow involvement, and can occur following the relapse of AML or during the progression of myelodysplastic syndrome (MDS), myeloproliferative neoplasms and chronic myelogenous leukemia. MS is frequently associated with AML (2). Occasionally, MS develops as an isolated lesion, with a wide variation in size and location, accounting for 2 cases per million adults (3). MS is described in ~9% of patients with AML as an early manifestation of the disease, or is in the relapsed setting, which is observed frequently after allogeneic hematopoietic stem cell transplantation (allo-HCT) (4). The diagnosis of MS is mainly based on clinical manifestations and cytochemical and/or immunophenotypic factors. Overall, 54-70% of patients with MS present with abnormalities at the molecular level, including positivity for myeloperoxidase (MPO), and nucleophosmin 1 and NRAS proto-oncogene GTPase mutations (5-7). In a previous study, the positive rates of MPO, CD43 and CD117 expression in 39 patients were 92.1% (35/38), 91.3% (21/23) and 42.3% (11/26), respectively, with high sensitivity (8). Previously, mutations in tumor protein p53 (TP53) were considered to occur at a relatively low frequency in sarcomas (9). This is mainly since mutations in TP53 were identified by sequencing only exonic regions in the DNA binding domain or by performing immunohistochemistry (IHC) to detect positive staining in p53-mutated tumors due to the long half-life of the mutant protein (10). However, recent whole-genome sequencing analyses have revealed more frequent alterations in TP53, including structural alterations in TP53 intron 1 (11). $TP53^{+}$-MS is often accompanied by complex chromosome karyotypes (4).

Due to the lack of research surrounding MS, the most effective modes of treatment remain unclear, and at present, the AML chemotherapy regimen is the most commonly used (5). It has been reported that 70% of osteosarcomas have structural variations or mutations of TP53 (10). In TP53-mutant AML, decitabine-based hypomethylation chemotherapy has certain advantages (4). One study showed a 100% response rate

in *TP53*mut AML and high mutation clearance with a 10-day regimen of decitabine (12). Allo-HCT treatment should be considered for recurrent patients or patients with bone marrow lesions (5). However, due to various changes in TP53, TP53 mutations/null are often used as therapeutic targets for patients with MS. TP53-null often uses inhibitors for wee1 kinase, Chk1 and equine-like kinase 1, and TP53 mutations often use inhibitors for PRIMA-1 and PRIMA-1Met to re-activate wild-type TP53 activity (10). This is often abandoned due to bone marrow suppression and other side effects. If not treated in time, almost all patients may develop systemic disease and experience progression to acute leukemia (13). The present study describes, to the best of our knowledge, the first case of an elderly patient with lymph node MS combined with TP53 (V173G) mutation, who eventually died of respiratory failure due to refractory pneumonia after treatment with a variety of antibiotics.

Case report

In September 2016, a 65-year-old male patient with a recurrent fever for >4 months was admitted to the First Affiliated Hospital of Zhejiang Chinese Medical University (Hangzhou, China). The patient presented with a fever of ~38˚C, accompanied by chills, fatigue and occasional abdominal pain. The fever subsided without medical intervention, but did return at irregular intervals. The physical examination revealed roughly soybean-sized lymph nodes in the bilateral neck, armpit and groin, with tough, clear boundaries. The patient had a >3-year history of a gastric antrum ulcer and was being treated with pantoprazole. The patient had suffered from malaria >30 years previously and had recent weight loss of ~10 kg.

The laboratory examination results showed the following levels: Platelets (PLTs), $39x10^9$/l (normal range, 125-350$x10^9$/l); white blood cells (WBCs), $3.2x10^9$/l (normal range, 3.5-9.5$x10^9$/l), hemoglobin (Hb), 62 g/l (normal range, 115-150 g/l); and reticulocytes, 3.5% (0.5-1.5%). High-resolution computed tomography (HRCT) of the lungs shows scattered inflammation in both lungs, with multiple enlarged lymph nodes in the mediastinum (Fig. 1). Primordial cells were recorded at 1% (normal, 0%) and Epstein-Barr virus DNA at $5.95x10^3$/ml (normal range, 0-$4x10^2$/ml). A B-scan and CT showed multiple enlarged lymph nodes in the neck, groin and mesentery (Fig. 2). Positron emission tomography-CT results indicated a diagnosis of lymphoma, and the maximum standardized uptake value of the lymph nodes was 4.3 (normal, <2.0) (Fig. 3). Bone marrow routine examination showed a granulocyte:erythroid cell ratio of 0.1:1 (normal range, 2-4:1) and occasional erythroid dysplasia. In October 2016, immunohistochemical analysis of the bone marrow and lymph nodes, performed in the Zhejiang Provincial Hospital of Traditional Chinese Medicine (Zhejiang, China), showed the following results: MPO^+, $CD117^+$, $CD20^+$, $CD79a^+$, $PAX\text{-}5^+$, $CD3^+$, $CD43^+$ and Ki-67 20% (Fig. 4). The immunohistochemical staining was performed as follows: Fresh tissues were cut into small pieces with a diameter not exceeding 5 mm, and fixed at 4˚C overnight with 4% paraformaldehyde (prepared with PBS and pre cooled at 4˚C). Conventional paraffin-embedded sections (2-μm thick) were created by slicing, baking for 15 min and then embedding at 75˚C for 15 min before deparaffinization and dehydration. The samples were stained with 0.5% hematoxylin for 1 min, and with 0.5% eosin for a few seconds, both at room temperature. Finally, the HE staining results were observed under an optical microscope. The slices were then soaked in sodium citrate solution and heated at 75˚C for 15 min for antigen retrieval. Sealing was performed with 10% sheep serum (cat. no. ZLI-9022; OriGene Technologies, Inc.) at room temperature for 1 h before removing the agent. Subsequently, sections were incubated with primary antibodies at 4˚C overnight and then treated with secondary antibodies at 4˚C for 20 min the next day. The positive signal was visualized with DAB reagents (OriGene Technologies, Inc.) and slices were counterstained with hematoxylin. The antibodies employed in the current study included CD117 (cat. no. ZA-0523; 1:50; bone marrow sample; Thermo Fisher Scientific, Inc.), MPO (cat. no. MA1-80878; 1:500; bone marrow sample; Thermo Fisher Scientific, Inc.), CD20 (cat. no. TA800385; 1:150; lymph node sample; OriGene Technologies, Inc.), CD3 (cat. no. TA800385; 1:150; bone marrow sample; OriGene Technologies, Inc.); CD79a (cat. no. TA800688; 1:150; lymph node sample; OriGene Technologies, Inc.), PAX-5 (cat. no. 1TA801884; 1:150; lymph node sample; OriGene Technologies, Inc.), Bcl-2 (cat. no. PA5-27094; 1:150; lymph node sample; Thermo Fisher Scientific, Inc.) and goat anti-rabbit IgG (H+L) (cat. no. A-11012; 2 μg/ml; Alexa Fluor™ 594; Thermo Fisher Scientific, Inc.). Bone marrow gene mutation detection performed by Shanghai Tissuebank Diagnostics Co., Ltd., showed the TP53 gene missense mutation V173G.

The patient presented with repeated bouts of low fever and chills, but the body temperature subsided without medical intervention, and antibiotic anti-infection treatment (2 g latamoxef, twice a day for 2 weeks and 2 g cefoperazone sodium, once every 8 h for 4 weeks) was ineffective. Re-examination of bone marrow routine (September and October 2019) showed that the proportion of erythroid dysplasia was higher than the initial result (10 days earlier in September 2019). The bone marrow chromosome examination report showed that the patient karyotype was 45,XY,-3,-5,-12,-18,+Mar-3[17]/46,XY[3] (Fig. 5). Combined with the aforementioned examination results, the patient was diagnosed with MDS-refractory anemia. In November 2016, lymphoma was considered to be the source of fever.10 mg lenalidomide and 10 mg prednisone twice a day were used for treatment for 21 days. However, the number of primordial cells increased after treatment, indicating that the disease was developing.

For further diagnosis, the pathology of the left cervical lymph node was sent to the Shanghai Cancer Center (Shanghai, China) for further immunohistochemical analysis in December 2016, performed as follows: Fresh tissue was cut into small pieces with a diameter of 2 mm, fixed at room temperature overnight with 4% paraformaldehyde (prepared with PBS and pre cooled at 4˚C) and dehydrated. Conventional paraffin sections (2-μm thick) were baked for 15 min on the surface, and embedded blocks made at 60˚C for 4 h before deparaffinization and dehydration. The samples were stained with 0.5% hematoxylin for 1 min and with 0.5% eosin for a few seconds, both at room temperature. Finally, the HE staining results were observed under an optical microscope. Slices were then soaked in sodium citrate solution and heated

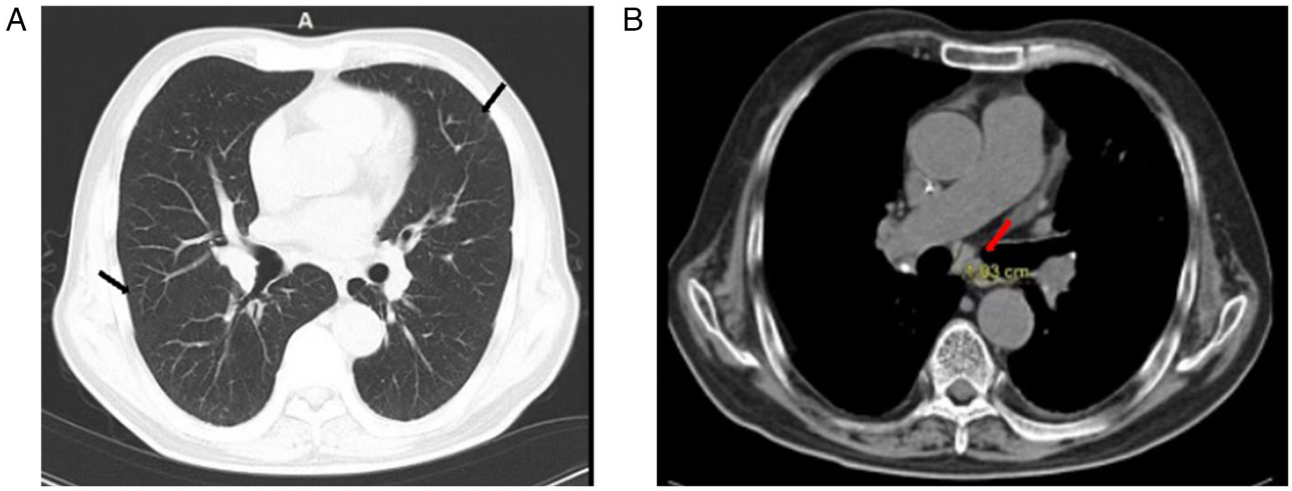

Figure 1. Lung high-resolution CT images. (A) CT image of the lung window showing scattered and small nodular high-density shadows (indicated by black arrows). (B) CT image of the mediastinal window showing multiple lymph nodes in the mediastinum, with a short diameter of 1.03 cm (indicated by the red arrow). CT, computed tomography.

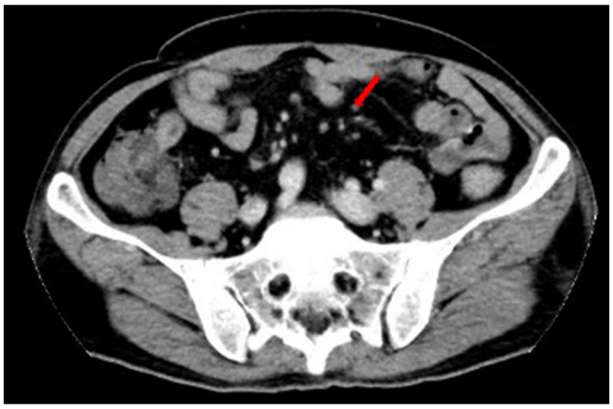

Figure 2. CT image. Full abdominal CT showing multiple small lymph nodes in the mesentery (indicated by the red arrow). CT, computed tomography.

at 60˚C for 4 h for antigen retrieval. Sealing was performed with 2.5% goat serum (cat. no. R37624) at room temperature for 45 min. Subsequently, sections were incubated with primary antibodies at 4˚C overnight and with secondary antibodies at 4˚C for 20 min the next day. The positive signal was visualized with DAB reagents (OriGene Technologies, Inc.) and slices were counterstained with hematoxylin at room temperature for 2 min. The antibodies employed included CD20 (cat. no. PA5-16701; 1:300); CD3 (cat. no. 14-0032-82; 1:100); CD43 (cat. no. 14-0039-82; 20 μg/ml), KP1 (cat. no. 14-0688-82; 1-5 μg/ml), CD117 (cat. no. 34-8800; 1:50), Ki-67 (cat. no. MA5-14520; 1:100), CD31 (cat. no. BMS137; 30 μg/ml) and donkey anti-rabbit IgG (H+L) (cat. no. A-21206; 1-10 μg/ml; Alexa Fluor™488) (all eBioscience; Thermo Fisher Scientific, Inc.). Due to the invasion of the lymph nodes by myeloid tumors, in combination with the medical history and results from the immunohistochemical analysis [$CD3^+$, $CD43^+$, $CD20^+$, $CD68/KP1^+$, $CD117^{-/+}$, $CD31^+$ and $Ki\text{-}67^+$ (~70%)], MDS was considered. Furthermore, ~70% of lymph node proliferative changes showed a large number of myeloid cells. Based on the aforementioned tests and combined with the symptoms of the patient, a diagnosis of MS with MDS was reached. Conventional chemotherapy regimens include induction remission chemotherapy and 2-3 cycles of consolidation chemotherapy for 2 months per cycle. In December 2016, the patient began the first induction remission chemotherapy for MS. In the first 3 days, 25 mg decitabine was used. From day 4 until day 11, 1 mg homoharringtonine and 12.5 mg cytarabine were administered twice a day.

After one course of chemotherapy, the PLT, RBC and WBC counts recovered, and analysis showed a WBC count of $4.3x10^9$/l, Hb levels of 124 g/l and a PLT count of $139x10^9$/l. Bone marrow routine showed active proliferation of bone marrow cells, and active proliferation and normal morphology of granulocytes and erythroid cells. A B-scan showed extensive lymph node reduction, suggesting complete remission (CR) after chemotherapy. In February 2017, the previous protocol was improved upon by adding 25 mg etoposide on day 4, followed by continuous use of homoharringtonine and cytarabine for 7 days. A PLT count of $43x10^9$/l was reported after chemotherapy. In April 2017, the use of decitabine was extended to 5 days, and the etoposide was changed to aclacinomycin at a dose of 20 mg once every other day for a total of 6 doses. The use of aclacinomycin and cytarabine was extended to 11 days, and the dose of homoharringtonine was increased to 2 mg. The PLT, Hb and WBC counts decreased significantly after this cycle of chemotherapy.

In April 2017, B-scan showed that the volume of right clavicle lymph nodes was larger than that at admission. In February and April 2017, bone marrow reexamination showed low bone marrow cell proliferation and the peripheral blood showed 10% primitive cells. This was considered to be the invasion of MS. The WBC count was severely reduced, and agranulocytosis was reported. The patient's inflammation index increased, a lung CT showed interstitial pneumonia and the diagnosis of pulmonary infection was clear. However, the pathogen was not identified by blood culture. Starting from April 2017, meropenem (1 g; 8 h once a day for 2 weeks) was used for anti-infection treatment, and empirical combination therapy with voriconazole (3 mg on the first day, and 200 mg

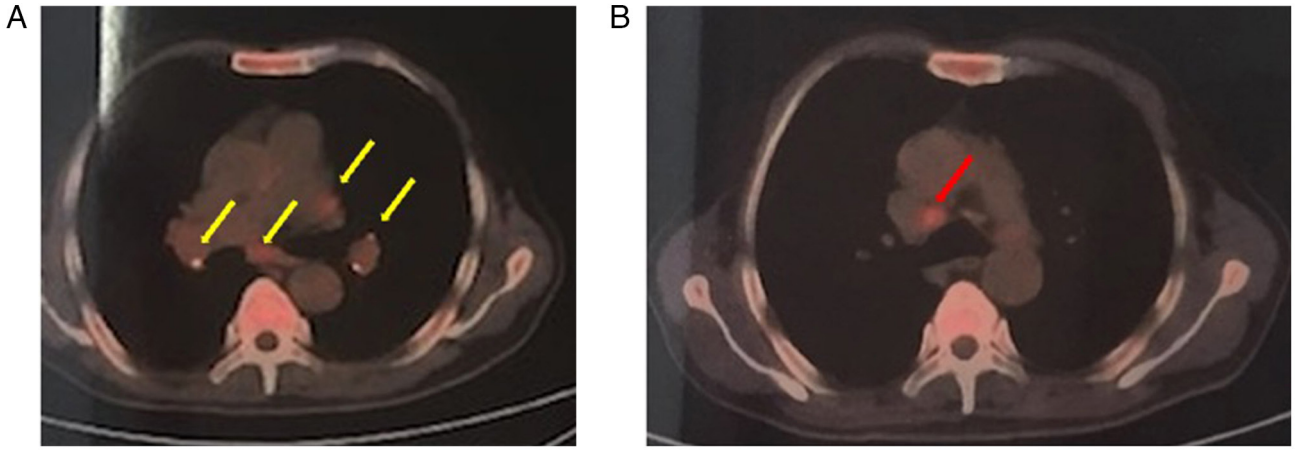

Figure 3. PET-CT image. (A and B) PET-CT images showing multiple lymph nodes in the bilateral mediastinum, lungs and liver hilum. (A) FDG metabolism is unevenly increased (indicated by the yellow arrows) and (B) the maximum standardized uptake value is ~4.3 (indicated by the red arrow). No significant abnormal increase in FDG metabolism was observed in the rest of the body. PET-CT, positron emission tomography-computed tomography; FDG, fluorodeoxyglucose.

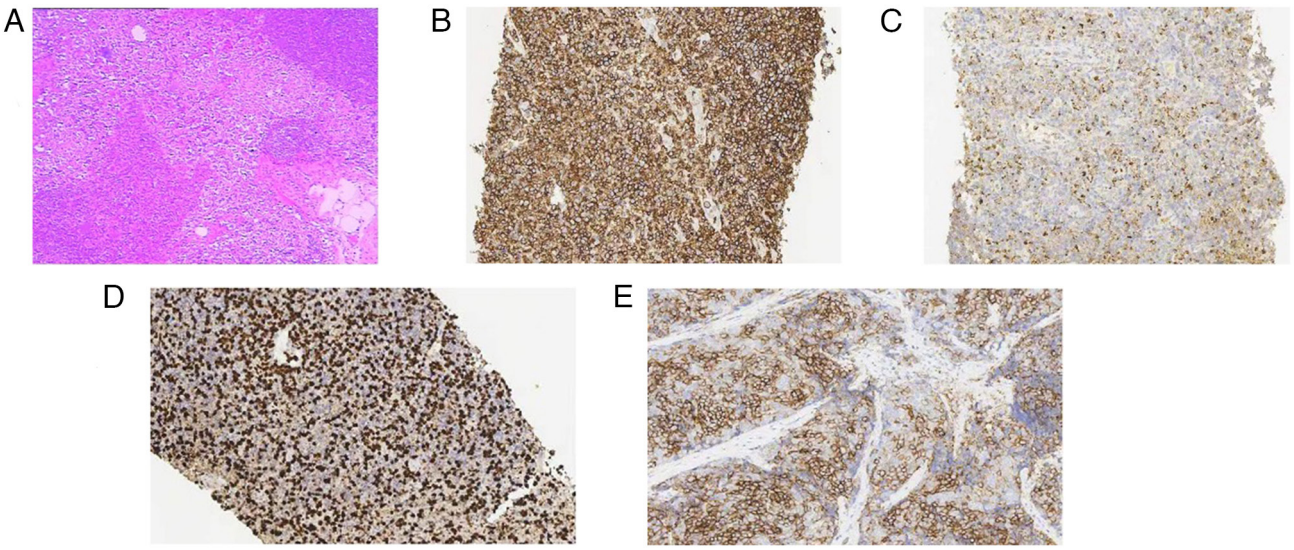

Figure 4. H&E and immunohistochemical images. (A) Diffuse infiltration of tumor cells with heterocysts (H&E staining; magnification, x10). (B) CD117(+) (magnification, x20). (C) Myeloperoxidase(+) (magnification, x20). (D) Ki-67(+) (magnification, x20). (E) CD117(+) (magnification, x20). H&E, hematoxylin and eosin.

orally thereafter, once every 12 h for 3 months) was used for antifungal treatment. Starting in June, treatment with vancomycin (1 g per day for 2 weeks) and amphotericin (20 mg per day for 1 month) was administered. Starting from July, cefoperazone sodium (2 g per day until death) and moxifloxacin (0.4 g per day for 2 weeks) were used for anti-infection treatment. After treatment, the inflammatory index did not decrease, but increased once again. Finally, the patient died of respiratory failure due to decreased oxygen partial pressure.

Discussion

As MS is mainly characterized by extramedullary soft-tissue masses that can occur in any part of the body, it is often misdiagnosed as lymphoma (14). A previous study reported that the misdiagnosis rate of MS is as high as 47%, and that of primary MS is even up to 75-86% (15). The diagnosis of MS mainly depends on the results of the pathological biopsy and immunohistochemistry. It has been reported that the most commonly expressed antigens in MS include CD43, CD68, lysozyme, MPO and CD117, with 66-69% of MS cases being MPO^+ (16,17).

Since the clinical manifestations of MS are not unique, most MS cases develop into acute leukemia soon after diagnosis, with a median time of ~7 months (5). Moreover, TP53-targeted drugs are still in clinical trials and have not yet shown much success due to significant side effects, including bone marrow suppression (18,19). Therefore, AML chemotherapy regimens, including idarubicin and cytarabine, and fludarabine, cytarabine, idarubicin and granulocyte colony-stimulating factor, are often the preferred therapy for MS (5). AML chemotherapy is required for both new-onset MS and other types of MS. Studies have shown that early intervention with chemotherapy can delay the progression of MS to AML (20,21). Older patients are often unfit for intensive chemotherapy, and for these cases,

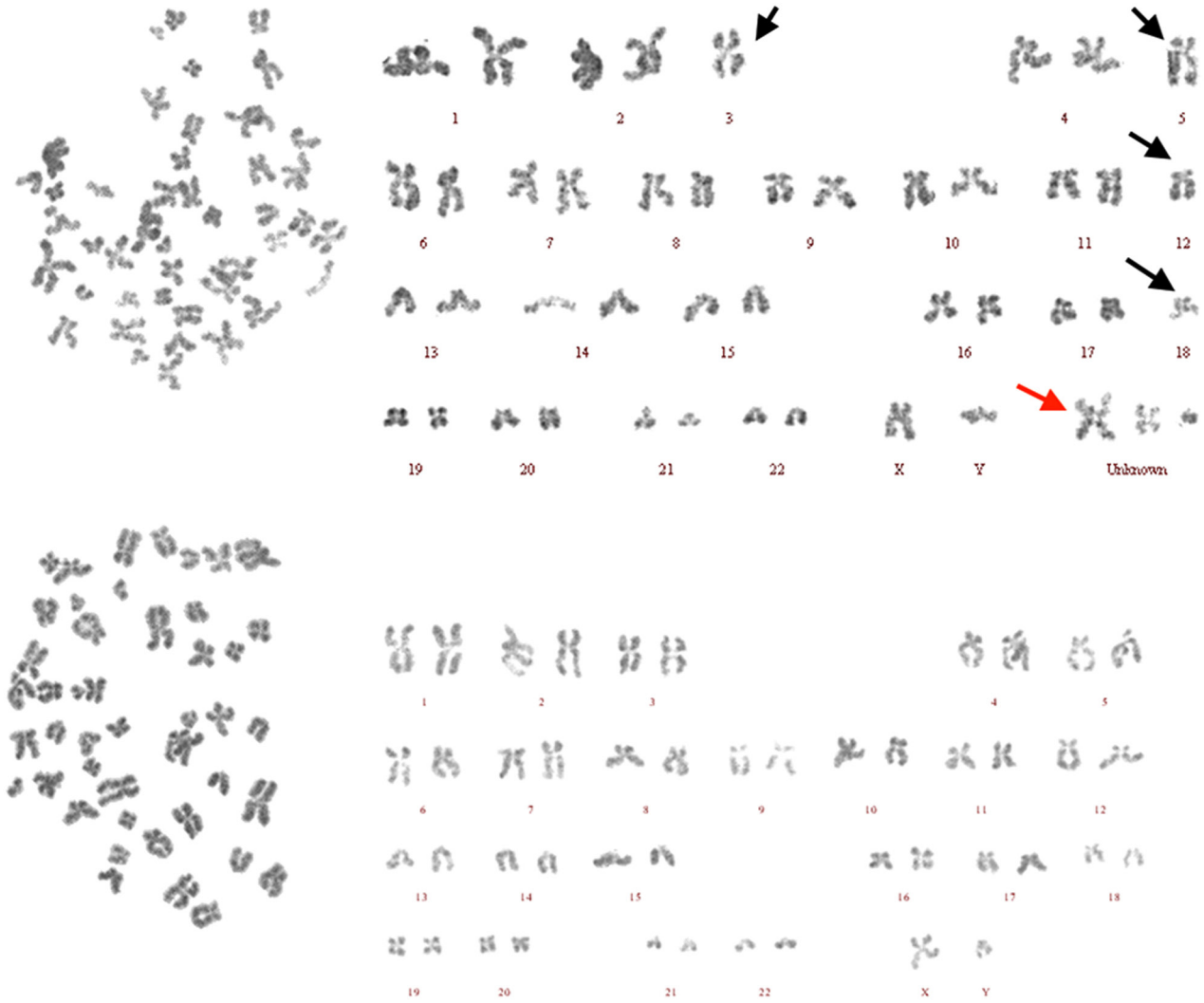

Figure 5. Chromosome images. Chromosome deletion (indicated by black arrows) and an unknown chromosome (indicated by the red arrow). The patient karyotype was 45,XY,-3,-5,-12,-18,+Mar-3[17]/46,XY[3].

epigenetic therapy with hypomethylating agents offers a small advantage over chemotherapy in TP53-mutant AML (22).

Decitabine is a deoxynucleotide analog that can selectively inhibit DNA methyltransferase, causing DNA hypomethylation and cell differentiation or apoptosis to exert antitumor effects. Decitabine is often used to treat elderly patients with AML or patients with high-risk chemoresistant phenotypes (23). Some studies have confirmed the efficacy of decitabine in the treatment of MS, reporting that it can induce long-term remission (4,24). In a Surveillance, Epidemiology and End Results database analysis, Liang *et al* (13) found that when using overall survival as an indicator of efficacy, patients with non-isolated MS showed an improved response to cytarabine-based AML chemotherapy regimens. It has also been reported that a patient with bladder MS with TP53 mutation achieved a significant improvement in symptoms and achieved complete CR in the first cycle of 20 mg decitabine treatment combined with induction chemotherapy. Due to the consideration of high-risk cytogenetics and TP53 mutations, subsequent allo-HCT was performed for consolidation (4). Similarly, the patient reported in the present study was treated with decitabine combined chemotherapy and achieved CR after the first chemotherapy. This indicates that decitabine combined with chemotherapy is effective in the induction therapy for MS with TP53 mutation. However, the treatment effect after CR varies between patients (3). Consolidation therapy after the induction of remission still requires future prospective randomized controlled trials to clarify the optimal treatment regimen.

In recent years, an increasing number of studies have recognized the importance of TP53 in tumors (25-27). p53 is a transcription factor that stabilizes genotoxic stress and induces the transcription of genes involved in cell cycle arrest, apoptosis and metabolism, thereby acting as a tumor suppressor (22). In general, tumor suppressors have a loss-of-function or deletion mutation in cancers (28). However, most TP53 mutations are missense mutations in the DNA binding domain, making mutant TP53 lose tumor suppressor functions and gain carcinogenic functioning independent of wild-type TP53 (29). TP53 is closely related to the genomic and chromosomal instability of osteosarcoma (30,31). However, no representative chromosome translocation has yet been found (32). The frequency of

complex karyotypes in TP53-positive patients is significantly higher than that in TP53-negative patients (33). At the molecular level, since TP53 mutations mostly occur in exons of the DNA binding domain, the arginine residue of the p53 protein is considered to be a mutation hot spot, which can affect DNA binding and change the activity of the mutant protein (25,26,34). TP53 is associated with chemosensitivity, mainly by affecting the patient's chemical tolerance or overall survival rate (27). Middeke *et al* (35) showed that TP53-positive patients have a high risk of recurrence after remission, and that allo-HCT plays an important role in post-remission treatment. However, few patients have access to this treatment. Therefore, TP53 mutation means that compared with patients with TP53-negative MS, patients with TP53-positive MS have low sensitivity to intensive chemotherapy, poor tolerance, short CR duration, high risk of recurrence after remission and complex cytogenetics.

The pathogenic V173G mutation of TP53 was first reported in a 2015 article on non-small cell lung cancer (NSCLC) (36). V173G is considered to make up 15% of all TP53 mutations in NSCLC, and is expected to be harmful and destructive. In 2021, the case of one young patient with florid cemento-osseous dysplasia and Li-Fraumeni syndrome, who eventually developed osteosarcoma, was reported. After biopsy, the p.V173G TP53 mutation was identified, and the allele frequency was high at 86% (37). It can be speculated that TP53 (V173G) is a feature of concurrent diseases that occur rarely and that it creates conditions for tumor development. However, the correlation between TP53 (V173G) mutation and the prognosis and development of tumors still needs to be further explored with large sample data.

Patients with MS who harbor TP53 (V173G) mutations and complex karyotypes are considered to have a poorer prognosis (38). In the present study, the patient had a TP53 mutation, an abnormal chromosome karyotype and poor cytogenetic characteristics, which were associated with a poorer prognosis. Disease recurrence occurred after the third cycle. Due to severe neutropenia and uncontrolled inflammation, the use of multiple antibiotics for treatment was ineffective. In the end, the patient developed severe pneumonia and died. It has been reported that the expression of TP53 is increased in drug-resistant NSCLC (39). It can be speculated that the refractory pneumonia of this patient may be related to the positive expression of TP53. A previous study found that TP53 positivity was associated with tumor lymph node metastasis (40). Patients with TP53-positive tumors have a higher rate of lymph node metastasis. In addition to genetics, the cause of recurrence may also be related to the invasiveness of the MS. One study has shown that MS-derived cell lines have type IV collagenase, which has been reported to be associated with a poorer prognosis in gastric cancer (41).

In conclusion, MS has a low incidence rate, poor prognosis and short survival time. The clinical manifestations of MS are not specific and are frequently misdiagnosed. MS should be considered in the differential diagnosis of suspicious masses or atypical cell infiltration with or without bone marrow involvement. If economic conditions permit, genetic testing is recommended while performing immunohistochemistry, and next-generation sequencing is a better choice than whole exome sequencing. TP53-positive MS should be awarded more attention in clinical practice due to its unsatisfactory prognosis and lower survival rate compared with that of TP53-negative MS.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MM and SD conceived the study, participated in the design of the study and collected the data and the images. MM drafted the manuscript, collected the clinical data and performed the literature research. SD participated in the data acquisition and interpretation, drafted the manuscript and critically revised the manuscript. MM and SD confirm the authenticity of all the raw data. Both authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent to publish the medical data and images for this case.

Competing interests

The authors declare that they have no competing interests.

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