Mediastinal Granulocytic Sarcoma

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Dan Cheng and Song Zhang

Granulocytic sarcoma (GS), also known as myeloid sarcoma, extramedullary myeloid tumor (EMT), is defined as an extramedullary tumor composed of immature granulocytic precursor cells and initially, named Chloroma because of the myeloperoxidase (MPO) in the tumor cells which leads to greenish cut surface. GS can occur at any site, with skin and lymph node being the most common sites of involvement, and followed by soft tissue, bone, periosteum, epidural structure, and infrequently gastrointestinal tract. The mediastinum and pericardium are unusual sites of manifestations. GS was originally described by Burns in 1811, but it was not until later in 1853, when it was investigated by King who reported it as "a green colored tumor." In 1966, Rappaport proposed the term "granulocytic sarcoma." The conception of extramedullary myeloid cell sarcoma (EMT) was mentioned in the year 1988 by Davery, including extramedullary infiltration of leukemia and isolated GS. In 2001, GS was classified as "myeloid sarcoma" in the classification of hematopoietic and lymphatic tumors. It was not until 2002, when the WHO declared the name "myeloid sarcoma." However, granulocytic sarcoma seems to be the most frequently used term, since around 30% do not show MPO positivity.

6.1 Classification

GS is divided into isolated GS (primary or nonleukemic GS) and GS of extramedullary infiltration (leukemic GS). Leukemic GS usually presents in acute myelogenous leukemia (AML), or appears after the onset of AML. Studies also find that it could occur in the blastic phase of chronic myelogenous leukemia (CML) or is a symptom of myeloid proliferative disease. However, GS as a performance before the onset of AML is rather rare. Nonleukemic GS means the bone marrow aspiration and biopsy reveal no hematological disease, which only present as focal solitary mass without obvious clinical symptoms and signs, does not progress into GS with AML in 30 days. Nonleukemic GS is a rare disease with an incidence of 2/1,000,000 in adults.

6.2 Pathogenesis

The pathogenesis of GS is linked to different chromosomal abnormalities. The commonest translocation is t(8;21)(q22;q22) and inv(16)(p13;q22), which are associated with extramedullary disease in AML. The prognosis of patients with them is worse than that of patients with normal karyotype. The prognosis of patients of GS with t(8:21) is worse than that of patients of primary AML with t(8;21). The survival rate of patients with chromosome 8 abnormality is lower than that of other abnormal karyotypes, and the median survival periods are significantly shorter, which indicates poor prognosis. The mechanism of GS in patients with inv(16) maybe due to the abnormal regulation of CBF transcription factors related to cell adhesion and recognition, but the details of this mechanism need to be studied. Other reported abnormalities in GS include del(16q), del(5q), del(20q), t(9;11), t(8;17), t(8;16), and t(1;11) and chromosome 4, 7, or 11 abnormalities.

The exact mechanism of extramedullary involvement is not fully understood. However, some studies have found different cytokine receptors and adhesion molecules control "the homing" of cancer cells to specific tissues. CD56, the blast neural adhesion molecule, may also play a role in the pathogenesis. Its role has been supported by the fact that a high incidence of GS has been associated with CD56 blast expression, common with t(8; 21). It is also believed that deregulation of core-binding factor transcription factors may

D. Cheng
Department of Respiration, Central Hospital of Haining, Zhejiang Province People's Hospital Haining Hospital, Haining, China

S. Zhang (✉)
Department of Respiratory and Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Shandong, China

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be part of the pathogenesis of GS, which are involved in cellular adhesion and recognition.

6.3 Clinical Features

GS occurs at any age, mostly in children and adolescents, without significant gender differences.GS may involve any anatomic locations, including skin, lymph node, bone, reproductive system, digestive system, and nervous system. Clinical presentation is dependent on tumor location with symptoms usually occurring as a result of a tumor mass effect or local organ dysfunction. The diagnosis of GS is challenging due to its various locations, clinical manifestations, imaging findings, and morphology, especially in patients without hematologic diseases, which are often misdiagnosed as lymphoma, histiocytic tumor, and various local solid tumors.

Rarely patients with GS may have temporarily relieved themselves for a period of time, and the cause is not clear. Most patients have a history of infection or blood transfusion before spontaneous remission, so some scholars put forward the hypothesis of spontaneous remission caused by infection and blood transfusion. Bacterial, fungal, and viral infections trigger the immune response, leading to activate immune reactions that increase the levels of tumor necrosis factor-α (TNF-α), interferon-γ (INF-γ), and interleukin-2 (IL-2), and activate NK cells, cytotoxic T cells and macrophages, thus induce cross immune response to control leukemia clone.

Lymph cells in unirradated blood have antileukemia effects. After blood transfusion, allogeneic lymphocytes can play the role of antileukemia just like the graft-versus-leukemia (GVL) in allogeneic transplantation.

There is some sort of association between clinical presentation and molecular abnormalities. GS with t(8;21) is most commonly found in the orbital region in pediatric patients, while adult patients with inv(16) show a higher incidence of gastrointestinal and breast. Cutaneous GS may be associated with trisomy 8, but this association is uncertain.

6.4 Diagnosis

Isolated GS is difficult to be diagnosed with routine HE staining, especially in patients with normal hematopoietic system. It appears as a proliferation of cancer cells including myeloblasts, monoblasts, or less frequently promyelocytes; accordingly, it is subdivided into granulocytic sarcomas, monoblastic, and myelomonocytic sarcomas. It is also divided depending on the degree of maturation of the cells into blastic, immature, or mature types. Blastic GS is primarily formed of myeloblasts with little maturation. Immature GS is composed of myeloblasts, promyelocytes, and eosinophilic myelocytes. Mature GS consists of promyelocytes, more mature cells, and abundant eosinophils.

The technology of immunohistochemistry can significantly improve the diagnostic accuracy of GS in pathology. Common antibody markers in immunohistochemical technique include MPO, lysozyme, CD43, CD68, CD3, CD15, CD34, and CD99. MPO is the specific marker in myeloid cell group, which is almost expressed in all myeloid cells and is not expressed in lymphoid cells. MPO is expressed in 66–96% of GS cases, which is used to differentiate GS from lymphoma. MPO is the most useful marker for GS recognition because of its high sensitivity and specificity to myeloid cells, but it is often not expressed in poorly differentiated blastic cell tumors. Lysozyme mainly exists in the cytoplasm of granulocytes and it is the most sensitive marker of myeloid cells, especially in poorly differentiated myeloid cells and is not crossly expressed in lymphoid cells. Although lysozyme also exists in some epithelial cells and carcinomas, it can be used to differentiate GS from lymphoma. CD68 is the hematopoietic differentiation marker in the macrophage–monocyte system. When myeloid cells differentiate into a monocyte system, CD68 is expressed in AML and CML. CD68 is commonly expressed positively in GS because monocytic leukemia tends to have extramedullary infiltration, but there are also GS with CD68 negative. CD43 is expressed in the surface of hematopoietic stem cells or progenitor cells and is the marker of T-lymphocytes, which is expressed in almost all GS with high specificity and low sensitivity. Only CD43 positive cannot be as a diagnostic basis of GS. When CD43 positive and CD3 negative tumor cells of undetermined origin are encountered, myeloid tumors should be considered. Therefore, the above four immunohistochemical antibody markers can provide an important basis for the diagnosis and differential diagnosis of GS. Other common antigens include CD117, CD11c, CD13, and CD33. To exclude other differential diagnoses, B- and T-lineage markers, especially CD20, CD45RO, CD79a, and CD3, should be tested.

6.5 Treatment

Surgical operation, local radiotherapy, systemic chemotherapy, and stem cell transplantation are often used in the treatment of GS. However, it has been reported that surgical treatment is still controversial which is only used to make a definite diagnosis with biopsy. Local surgical resection may possibly speed up the transformation from GS to AML. But surgical resection is still necessary to relieve local symptoms of GS in the important locations such as vertebral canal or brain, which causes nerve compression symptoms and seriously affects the quality of life of the patients. Local recur-

rence rate with only surgical treatment is higher than that of surgery combined with chemotherapy. Most GS patients are relatively sensitive to local radiotherapy and have a good therapeutic effect, but it cannot delay the transformation of GS to AML, or improve the disease-free survival and overall prognosis of GS.

Systemic therapy represents the mainstay of treatment even in isolated GS given the majority (71–100%) of patients treated with localized methods (surgery and/or radiotherapy) progress to acute leukemia. Chemotherapy should be recommended in all cases, including after complete resection of isolated GS. A variety of chemotherapy regimens used in AML remission induction have been used in GS including Idarubicin and Cytarabine; Fludarabine, Cytarabine, Idarabucin, and G-CSF(FLAG); Cyclophosphamide, Cytarabine, Topotecan, and G-CSF (CAT-G); and Daunorubicin and Cytarabine; which have been shown to induce complete remission in up to 65% of patients and achieve a median survival of 40 months. The comparison of these different chemotherapy regimens in the setting of GS is very limited in the literature. GS is more likely to be resistant to chemotherapy drugs than AML, leading to a higher recurrence rate.

Recently, it has been reported that allogeneic stem cell transplantation may be a very effective treatment for primary GS and improve prognosis. Reports of GS secondary to CML were few. CML complicated with GS usually indicates the progress of disease, short survival time, and high mortality. Tyrosine kinase inhibitor and allogeneic stem cell transplantation are the prime treatment choices.

6.6 Prognosis

At present, most clinical studies show the prognosis of GS is poor, and its 2-year overall survival rate is only 6%. The prognosis of isolated GS is better than that of GS with AML, but the patients tend to develop to AML, especially the patients without regular treatment after diagnosis, generally develop to AML within 10 months after the diagnosis of GS. Therefore, we should pay attention to monitoring the bone marrow image of GS patients, if necessary, should be multiple sites puncture, and long-term follow-up.

6.7 Case Analysis

6.7.1 Case 1

A 20-year-old man complained of cough, expectoration, and bloody sputum for half a month. The patient was diagnosed with AML 3 years ago and had 10 cycles of chemotherapy. The last chemotherapy was made 10 months ago.

Chest CT: A heterogeneously enhancing mass occupied the right anterior mediastinum with pericardial and pleural effusion (Fig. 6.1).

[Diagnosis] Mediastinal granulocytic sarcoma

[Diagnostic basis] Anterior mediastinal mass combined with a history of AML, mediastinal GS should be considered. CT-guided biopsy confirmed the diagnosis of GS (Fig. 6.2). Immunohistochemistry demonstrated positivity for LCA, MPO, CD34, CD117, Lysozyme and TdT, and negativity for CK, CD3, CD5, CD20, and S-100.

[Analysis] GS is defined by the WHO as a tumor consisting of myeloid blasts with or without maturation occurring at an anatomic site other than the bone marrow. Mediastinal GS is rare and may be difficult to discriminate from other mediastinal tumors. No unique chromosomal abnormalities are associated with mediastinal GS; however, most cases of AML-associated mediastinal GS have the FAB Classification M1, M2, and M5 morphology. Ramasamy et al. [1] reported that 93% of patients with mediastinal GS and concurrent AML have peripheral blood circulating blasts. Nounou et al. [2] have reported an

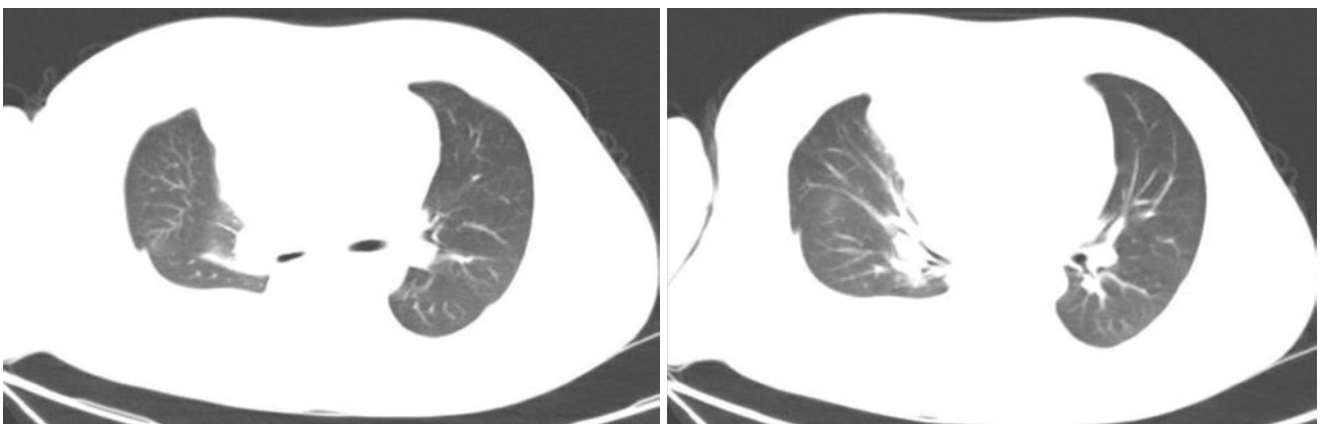

Fig. 6.1 Chest CT images of a 20-year-old man complained of cough, expectoration, and bloody sputum for half a month

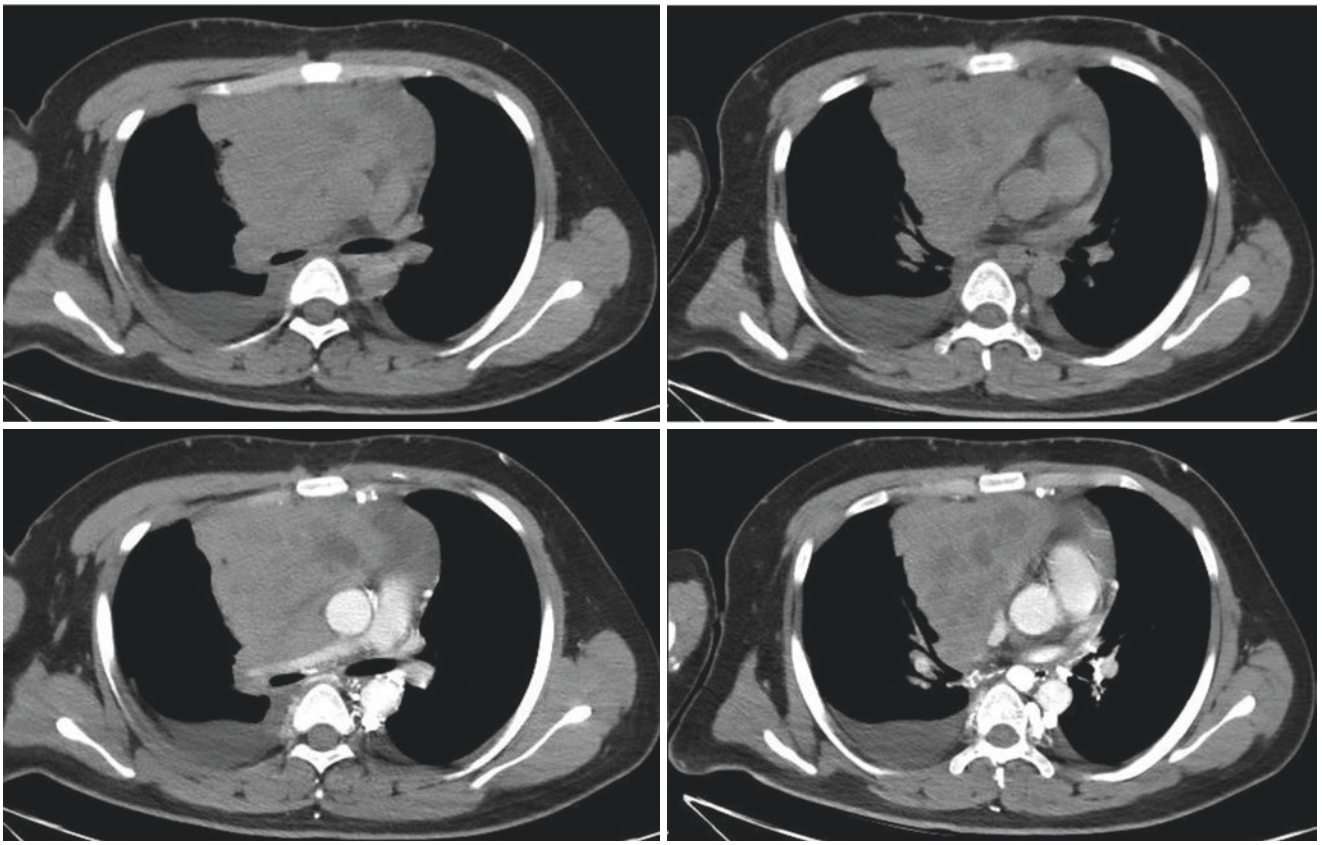

Fig. 6.1 (continued)

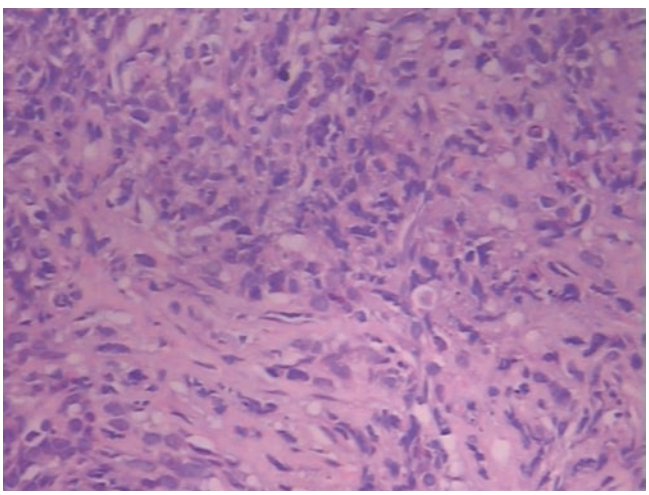

Fig. 6.2 The pathological feature of GS

increase in the incidence of triploid and tetraploid chromosomal abnormalities associated with mediastinal GS. Peripheral blood blasts or chromosomal abnormalities might be one of the useful diagnostic factors of mediastinal GS, indicating whether it is an operable case, such as thymoma.

The European Society for Haematology recognizes a variety of extramedullary manifestations of myeloid neoplasms: (1) GS with concurrent acute myeloid leukemia (AML); (2) extramedullary relapse of AML, including in the post-bone marrow transplant setting; (3) blast phase/transformation of a myeloproliferative neoplasm or chronic myelomonocytic leukemia; (4) isolated GS, which occurs in association with a normal bone marrow biopsy and blood film, and in the absence of any history of myeloid neoplasia. GS develops in 2–8% of cases of myelocytic leukemia. In AML, GS may be the first manifestation of AML that may precede the clinical disease by even months to years. The same might happen during relapse, and GS becomes the initial presentation of relapse in a treated AML patient after remission.

Demographically, GS has a slight male predominance with a male-to-female ratio of 1.2:1; also, it may occur at any age and any site in the body. Mediastinal GS generally has no obvious symptoms. When it compresses or invades the surrounding organs, it will produce corresponding symptoms, such as chest tightness and cough due to tumor compression of bronchi and lung, esophageal obstruction, pericardial, and pleural effusion, superior vena cava syndrome. Compared with other mediastinal tumors, there is no specific symptom.

GS pathology showed that most of the cells were immature granulocytes. The cells were round and oval, rich in cytoplasm, similar to lymphoma. Immunohistochemistry is helpful for diagnosis and differential diagnosis. CD2 and

CD3 are the markers of T cell line expression, and their negative results can exclude T cell line tumor; CD20 and CD79a are the markers of B cell line expression, and their negative results can exclude B cell line tumor; MPO positive indicates GS. When clinicians suspect GS, they should check blood and bone marrow to eliminate leukemia. For peripheral blood, bone marrow smear and bone marrow biopsy without leukemic changes, immunohistochemistry is of great significance in the diagnosis of the disease.

6.7.2 Case 2

A 61-year-old woman complained of chest tightness and shortness of breath after activities for a month.

Chest CT: A heterogeneously enhancing mass occupied in the anterior mediastinum with infiltration surrounding structures. Right hilar and mediastinal lymphadenopathy and right pleural effusion could be seen (Fig. 6.3).

[Diagnosis] Mediastinal granulocytic sarcoma.

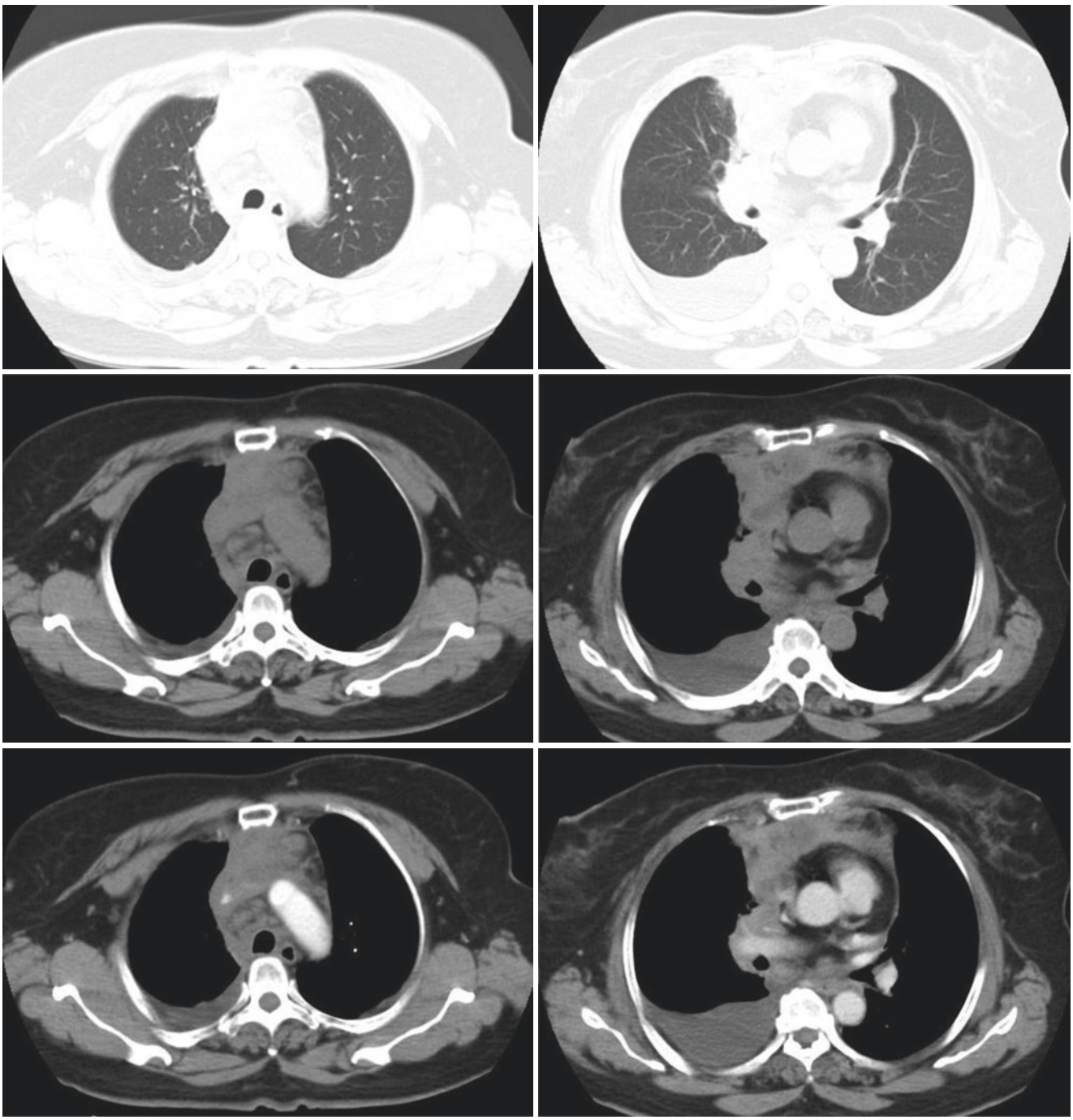

Fig. 6.3 Chest CT images of a 61-year-old woman complained of chest tightness and shortness of breath after activities for a month

[Diagnosis basis] Lymph nodes were biopsied with mediastinoscopy. The pathological diagnosis is mediastinal GS. Immunohistochemistry demonstrated positivity for CD3, CD20, MPO, CD117, CD68, CD43, CD34, and CD23, and negativity for Cyclin D1, CD10, TdT, and CK. The staining index for Ki-67 was about 90%. Pleural fluid staining showed a scattered population of hematopoietic cells intermixed with reactive cells. Bone marrow examination did not show any evidence of leukemia. A final diagnosis of extramedullary GS with malignant pleural effusion was made.

[Analysis] Diagnosis of GS with known AML or other hematologic malignancies is relatively easy but the differential diagnosis of primary GS is relatively difficult for a pathologist. Meis et al. reported a misdiagnosis rate of 75%, and the most frequent misdiagnosis is large cell lymphoma. More recent series, the rate of misdiagnosis has been found to be lower with a range of 25–47%. The patients were mostly mistaken for malignant lymphoproliferative disorders. The misdiagnoses are non-Hodgkin lymphoma, histiocytic lymphoma, thymoma, myeloma, eosinophilic sarcoma, extramedullary hematopoiesis, mucosa-associated lymphoid tissue, Ewing sarcoma, and carcinoma, and they could not be corrected until acute leukemia was suspected by bone marrow aspiration and biopsy or peripheral blood smears. Tissue biopsy is the preferred method. The morphologic appearance on H&E varies according to differentiation of the cells. It mostly consists of infiltration by myeloblasts. It is recommended to send the specimen to immunohistochemistry, flow cytometry, fluorescence in situ hybridization, and molecular analysis. Following the diagnosis of GS, bone marrow biopsy and aspiration should be performed to rule out other hematological malignancies.

GS is difficult to differentiate from lymphoma in pathomorphology, especially when there is no evidence of peripheral blood and bone marrow. It is more likely to be confused with NHL, such as lymphoblastic lymphoma, diffuse large B-cell lymphoma, and Burkitt lymphoma. B and T immunophenotypes are expressed in lymphoma. TdT is expressed in lymphoblastic lymphoma. Though a small number of GS tumor cells can also express TDT, but MPO and lysozyme are not expressed in lymphoma. When the tumor cells are similar to NHL, and the expression of B and T cell-related antigen is negative, or only CD43 is positive, the diagnosis of GS should be considered.

GS is difficult to be differentiated from extramedullary lesions of chronic myeloid proliferative diseases without primitive cells. Chronic myeloid proliferative diseases often occur in lymph nodes, showing the aggregation of mesophilic granulocytes and more mature granulocytes in the lymph sinus, adjacent parenchyma, and around blood vessels, without typical primitive cells and CD34 positive cells, which is the main differentiating feature from GS. Mediastinal GS is easily misdiagnosed as thymoma, metastatic tumors, or germ cell tumors. Clinicians should strengthen the understanding of the disease and reduce misdiagnosis.

Isolated GS in the absence of other features of AML is an unusual manifestation. Since patients receiving only local treatment have a high probability of progression to AML, management of GS should be on the lines of systemic disease. Imrie et al. [3] reported that within a median time of 7 months, 71% of GS patients who did not receive antileukemic chemotherapy subsequently developed AML. Malignant pleural effusions are rare in patients with AML. This case illustrates the rare presentation of GS, including mediastinal mass and malignant pleural effusion.

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