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Case Report

An 88-year-old man with MDS/MPN-RS-T accompanied by unexplained repeated pleural effusion

Miaoxin Peng[1*], Yipeng Ling[1*], Peipei Xu[1], Yueyi Xu[1], Ting Xie[1], Yonggong Yang[1], Bing Chen[2]

[1]Department of Hematology, Drum Tower Hospital, School of Medicine, Nanjing University, Nanjing, Jiangsu, China; [2]Department of Hematology, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University, Nanjing, Jiangsu, China. [*]Equal contributors.

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Abstract: Herein is described a case of an 88-year-old man with newly-typically diagnosed MDS/MPN-RS-T accompanied with gene mutations: SF3B1, JAK2V617F, TET2 and ASXL1. Moreover, the patient repeatedly developed unexplained pleural effusion. The pleural effusion was asymmetric, non-neoplastic, and lymphocytes dominated the transudate. After several times of drainage procedure for pleural effusion and the use of hydroxyurea and EPO along with supportive treatment, the patient got an extent of alleviating. To the best of our knowledge, this is the first report of a patient with the much rare disease of MDS/MPN-RS-T accompanied by an even rarer manifestation showing the repeated pleural effusion. Fortunately, the patient improved after our clinical treatment.

Keywords: Hematological malignancy, MDS/MPN-RS-T, pleural effusion, thoracentesis, myelodysplastic syndrome, clinical management

Introduction

Myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) became a full entity under the 2016 World Health Organization (WHO) classification, which is previously provisionally known as refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T) in WHO 2008. Gene mutations in patients with MDS/MPN-RS-T include: SF3B1 (~85%), JAK2V617F (~50%), TET2 (~25%), ASXL1 (~20%), DNMT3A (~15%), and SETBP1 (~10%) [1, 2]. Approximately 50% of patients harbored both the JAK2V617F and SF3B1 mutations, providing an intriguing genetic explanation for the hybrid nature of MDS/MPN-RS-T as being between an MDS and an MPN. Herein is described an 88-year-old man with newly diagnosed MDS/MPN-RS-T accompanied by the above representative molecular performance. In clinical practice, pleural effusion in hematological malignancies is rare when compared with solid tumors. Pleural effusions in patients with hematological malignancy are most often due to infection and to a lesser extent malignant infiltration of the pleura. Pleural effusions with MDS or MPN is much few. In this case, the reason of effusion is neither infection nor malignant invasion in lung. Briefly, MDS/MPN-RS-T is an extremely rare disease, making it far rarer when combining unusual manifestations. Here, the first case of atypical MDS/MPN-RS-T with repeated pleural effusion is reported.

Case report

In June 2017, an 88-year-old man was admitted to our Department of Hematology because of an incidental discovery of anemia and dramatically thrombocytosis. Over the decades, the man was in a very good health without diabetes, hypertension or any other chronic conditions of aging until nowadays. So, this is the first time for him to receive a comprehensive inspection.

At the outset, the patient had no symptoms. An initial basic examination as follows: the temperature was 36.7°C, the blood pressure 125/69 mmHg, the pulse 72 beats per minute, the respiration rate 18 breaths per minute, and the

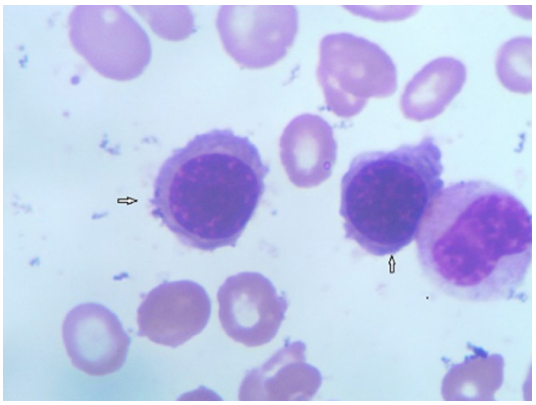

Figure 1. Dyserythropoiesis with megaloblastic changes Bone marrow, May-Grünwald-Giemsa (MGG) staining, 100×.

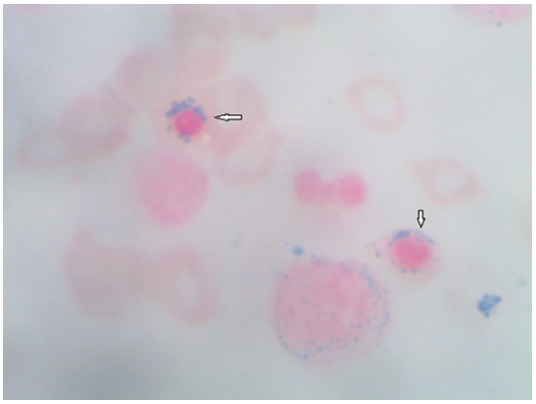

Figure 2. Ring sideroblasts. Bone marrow, Perls' staining, 100×.

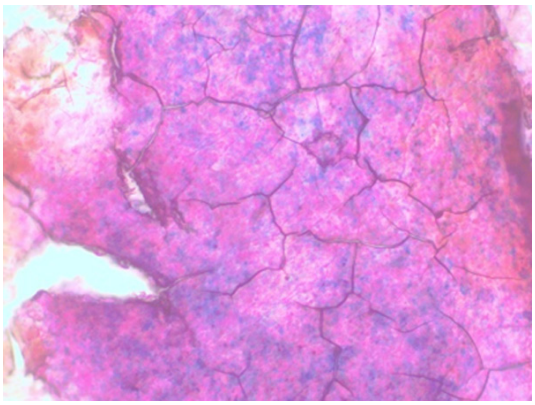

Figure 3. Extracellular iron (the blue background), Bone marrow, Perls' staining, 100×.

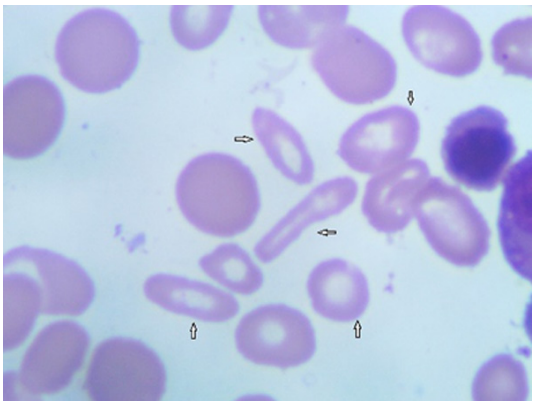

Figure 4. Mature red blood cells with unequal size and different shapes in Bone marrow, May-Grünwald-Giemsa (MGG) staining, 100×.

oxygen saturation 97-100% while he was breathing ambient air. Physical examination: pale appearance, a low breathing tone in lower left lung, splenomegaly at 3~4 cm below the costal margin, the remainder was approximately normal. Lab examination: A complete blood count (CBC) revealed the following results: Hemoglobin (Hb), 8.0 g/dl (normal range, 13.0-17.5 g/dl); hematocrit, 25.7% (normal range, 40-50%); mean corpuscular volume (MCV), 73.0 fl (normal range, 82-100 fl); platelet count, 1005×10^9/L (normal range, 125-350×10^9/L); and white blood cell (WBC) 17.1×10^9/L (normal range, 3.5-9.5×10^9/L) with a slightly elevated neutrophils 81.7% (normal range, 40-70%). Serum iron: 30.3 umol/L (6.6-28.3); serum ferritin: 420.30 ng/ml (22-322); Serum erythropoietin (EPO): 67.4 mIu/ml (4.3-29); BNP: 89 pg/ml (5-100); Blood Biochemistry: lactic dehydrogenase (LDH) 489 IU/L (normal range 109-245 IU/L), liver and kidney tests as well as electrolyte were in normal ranges. Echocardiography: Pulmonary Arterial Hypertension (PAH) 80 mmHg, EF 56%. BM aspirate: hypercellularity, granulocytic lineage 57% with 1% myeloblasts, erythroid lineage 35.5%, with dyserythropoiesis (megaloblastic changes and RS, **Figures 1** and **2**). Extracellular iron (**Figure 3**): ++, I: 1%, II 3%, III 9%, IV 21%, Ringed sideroblasts 59%. Mature red blood cells are of unequal size and different shapes (**Figure 4**) with an extremely light staining in central pale area. BM biopsy: hypercellularity, basically no adipose tissue, polymorphous megakaryocytes and dysmegakaryopoiesis like that of ET, extensive fibrosis about 1/2 of the total area. Cytogenetic exam: 46,XY [20]; BM-PCR: JAK2 (V617F) mutation: positive. BCR-ABL, CALR, MPL: negative. PDGFRα/β: negative. Next-generation sequencing in bone marrow sample (**Figure 5**):

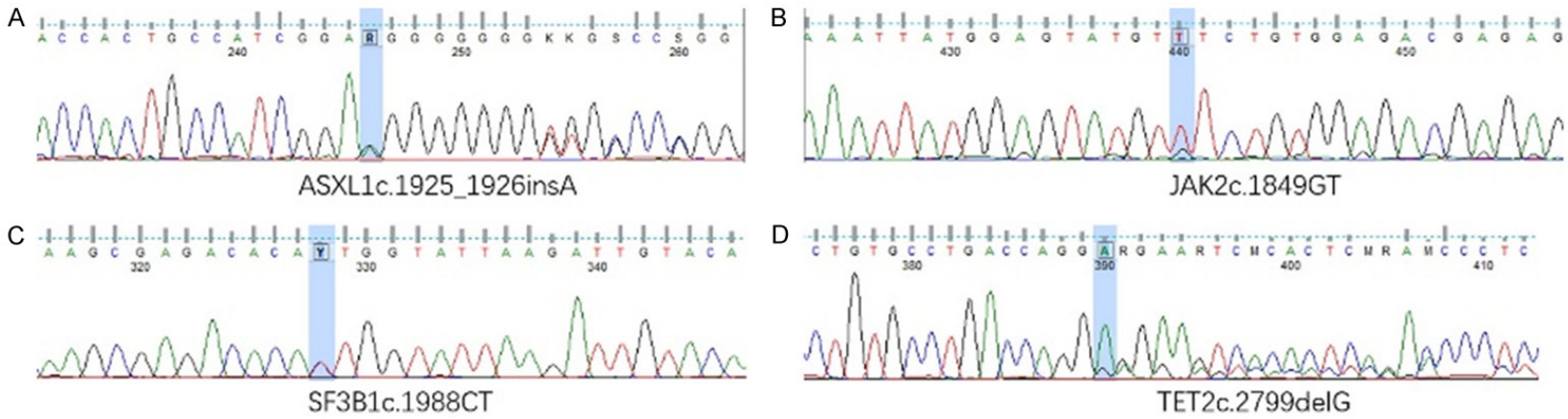

Figure 5. Next-generation sequencing: four mutations in BM sample. A: A frameshift mutation in ASXL1 gene: c.1925_1926insA (p.Gly643ArgfsTer15); B: A missense mutation in JAK2 gene: c.1849G>T; C: A missense mutation in SF3B1 gene: c.1988C>T; D: A frameshift mutation in TET2 gene: c.2799delG (p.Gly934GlufsTer19).

Table 1. CBC* results of the patient in different stages

Variable	Reference Range, Adults	First visit June 2017	After Hu July 2017	Outpatient August 2017	Second visit September 2017	Third visit May 2018	After ESA* July 2018
White-cell count (per mm^3)	3500-9500	17,100	2800	3420	4300	7300	10,100
Differential count (%)							
Neutrophils	40-70	81.7	64.1	67.0	70.1	77.3	79.6
Lymphocytes	20-50	7.8	17.4	25.4	13.4	10.7	12.9
Monocytes	3-10	7.8	11.4	3.8	13.8	9.3	2.6
Eosinophils	0.4-8	2.1	6.4	2.1	2.5	2.6	2.0
Basophils	0-1	0.6	0.7	1.7	0.2	0.1	2.9
Hemoglobin (g/dl)	13-17.5	8.0	5.4	7.3	5.9	7.4	10.7
Hematocrit (%)	40-50	25.7	16.6	22.4	18.3	23.9	30.5
Mean corpuscular volume (fl)	82-100	73.0	74.8	79.2	82.8	80.2	72.2
Platelet count (per mm^3)	125,000-350,000	1,005,000	153,000	1,217,000	780,000	789,000	576,000

*CBC (complete blood cell count). ESA (erythropoiesis stimulating agents).

a missense mutation in SF3B1 gene: c.1988C>T (heterozygous, frequency 43.11%); a missense mutation in JAK2 gene: c.1849G>T (heterozygous, frequency 60.56%); a frameshift mutation in TET2 gene: c.2799delG (p.Gly934GlufsTer19) (heterozygous, frequency 72.92%); a frameshift mutation in ASXL1 gene: c. 1925_1926insA (p.Gly643ArgfsTer15), four mutations are all related with myeloid hematopathy.

After a definitive diagnosis of MDS/MPN-RS-T, the patient mainly accepted supportive treatments including transfusion support, cytoreductive therapy (hydroxyurea for dynamically adjusted doses) and antiplatelet therapy. Initially, aspirin was not provided because of his persistent positive fecal occult blood. One month later, he was given aspirin 100 mg daily after fecal occult blood turn negative. After a while, the WBC and PLT were gradually declined, but Hb had no significant change under the circumstances of no use of erythropoiesis stimulating agents (ESA) at the beginning. Surprisingly, a significant improvement of Hb was observed when he accepted ESA (40,000 Unit ih biw) since May 2018. The CBC results are shown in **Table 1**.

Notably, the patient had no oppression in chest or any other respiratory symptoms, but had a low breathing tone in lower left lung at his first visit. Computed tomography (CT) of the chest showed: bilateral pleural effusion, especially noticeable on the left. Thoracocentesis and chest drainage was adopted by once central venous catheter. For a time, the hydrothorax were mitigated (**Figure 6**). However, the hydrothorax and chest distress appeared repeatedly in October 2017 and May 2018 (**Figure 7**). Every time after thoracocentesis and chest drainage, the patient got much better. However, several month later, the pleural effusion developed again. Flow cytometry of hydrothorax showed as (**Figure 8**): Lymphocytes account for about 80~90% of total cells. Exfoliocytology examination of the effusion: mainly lymphocytes with several histocytes and mesothelial cells and the final pathological diagnosis of the effusion (many times): No tumor cells were seen (**Figure 9**). Next-generation sequencing in pleural effusion sample: negative. No gene mutation was detected.

Three routine examinations of pleural fluid showed (**Table 2**) Acid-fast bacilli, ADA and T-Spot in hydrothorax were all negative. After the last visit, the patient did not back to hospital. According to the telephone follow-up, the old man reports a basically normal life.

Discussion

Pleural effusions are rarely observed in patients with hematological malignancy such as acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL) and MDS/MPN. Therefore, the underlying etiology of pleural effusions has not been well studied. Reviewing past literature, the etiology of pleural effusions in hematological malignancy including: 1) Infections. In a retrospective review [3] of a 10-year series cases of 111 patients with pleural effusion in

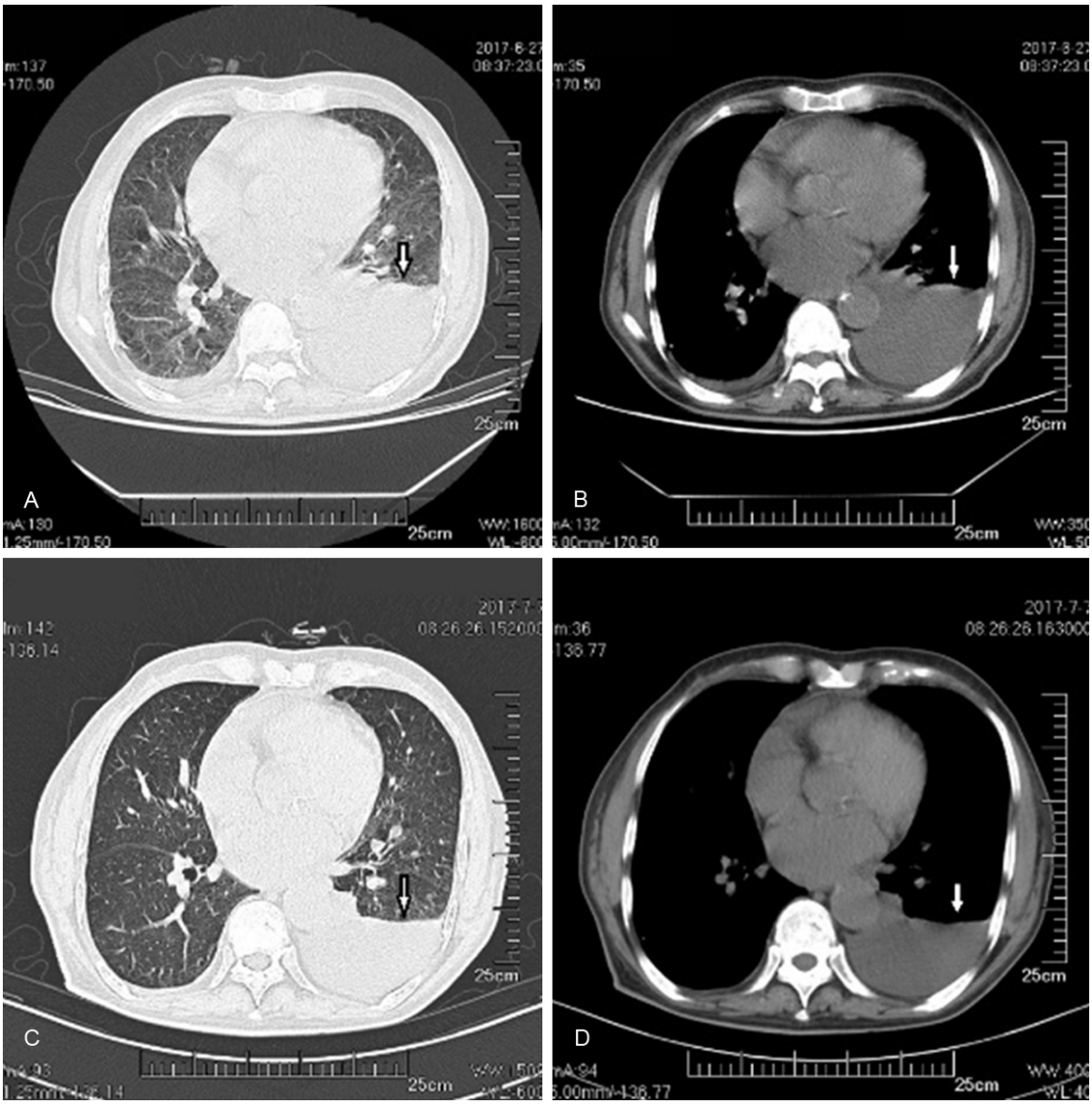

Figure 6. Computed tomography (CT) of the chest in June 2017 at the first hospitalization. (A) Lung window and (B) mediastinal window before thoracentesis and drainage (the arrows: left pleural effusion). (C) Lung window and (D) mediastinal window after thoracentesis and drainage (the arrows: pleural effusion was reduced).

leukemia and MDS from 1997 to 2007, the most frequent cause was infection (47%) followed by malignancy (36%). Similarly, earlier autopsy series for acute leukemia also describe parapneumonic effusions as the most common cause [4]. Overall, infection was predominant cause of pleural effusions followed by 2) Hematologic Malignancy. Malignant pleural effusions (MPEs) may occur at any time during the course of hematologic malignancies and may signal the presence of disease or indicate relapse [5, 6]. Lymphomas are the most common hematologic malignancies associated with pleural effusions, and may occur in 30% of Hodgkin lymphoma and in up to 20% of non-Hodgkin lymphoma, but they are rarely the sole manifestation in either [7]. Descriptions of pleural effusion in MDS are rare. Chronic myelomonocytic leukemia (CMML) represents the majority of patients with pleural effusions in the MDS category [8, 9]. Meanwhile, MPEs always show a bloody or chylous character with a positive cytology and/or molecular biology. 3) Therapy-related. In CML, the use of dasatinib is accompanied by a high incidence of pleural effusion, in those cases attributed to dasatinib-induced toxicity. ATRA syndrome is another complication of treatment of APL that can be

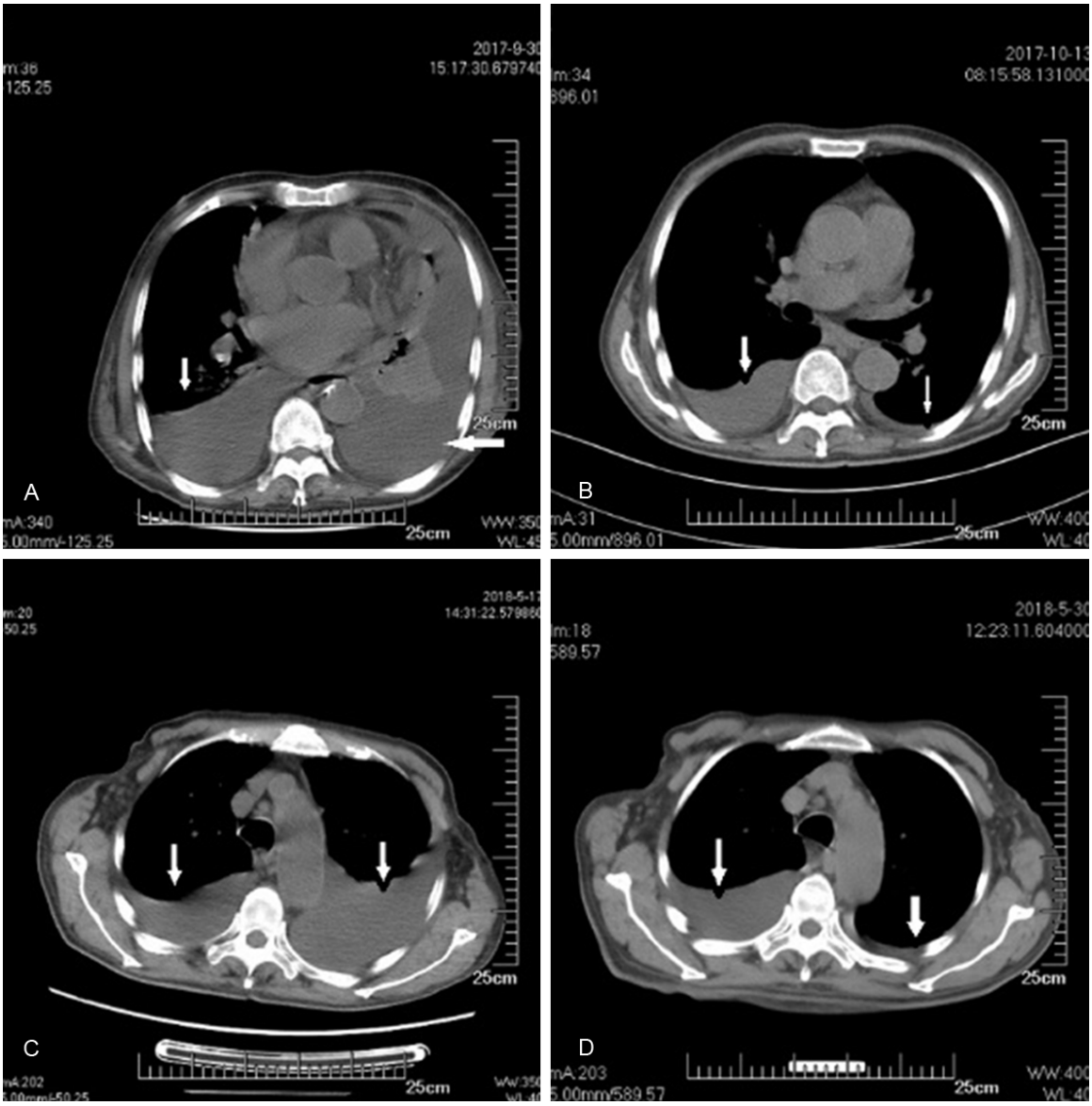

Figure 7. Mediastinal window of the chest CT scans at the second and third hospitalization. (A) Mediastinal window before and after (B) thoracentesis and drainage at the second hospitalization (pleural effusion was significantly reduced on both sides). (C) Mediastinal window before and after (D) thoracentesis and drainage at the third hospitalization (pleural effusion was reduced especially in left side).

associated with pleural effusion [10]. Similarly, other agents used in the treatment of leukemia and MDS such as fludarabine, cyclophosphamide and decitabine etc. may also cause pleural effusions [11]. In this case, the patient didn't receive any treatment before and had no evidence of infection. Subsequently, extramedullary infiltration was our first suspicion at one time. But the pleural effusion had no evidence of malignancy considering the effusion was nonspecific lymphocyte dominated transudate (since this disease is a lesion of erythrocytes and megakaryocytes), and the exfoliocytology and molecular biology were all negative, as well as many times of the routine examinations on effusion. Combining all the results, it was believed that the effusion had no connection with hematologic malignancy. Attention was also paid to other rare reasons as below 4) Immune mechanisms. Autoimmune manifestations associated with myelodysplasia are known as "autoimmune paraneoplastic syndrome" whose clinical presentation can include pleural effusion. Autoimmune disorders were diagnosed in 30 patients (7.4%) of 221 patients treated for MDS reported by Enright [12]. It

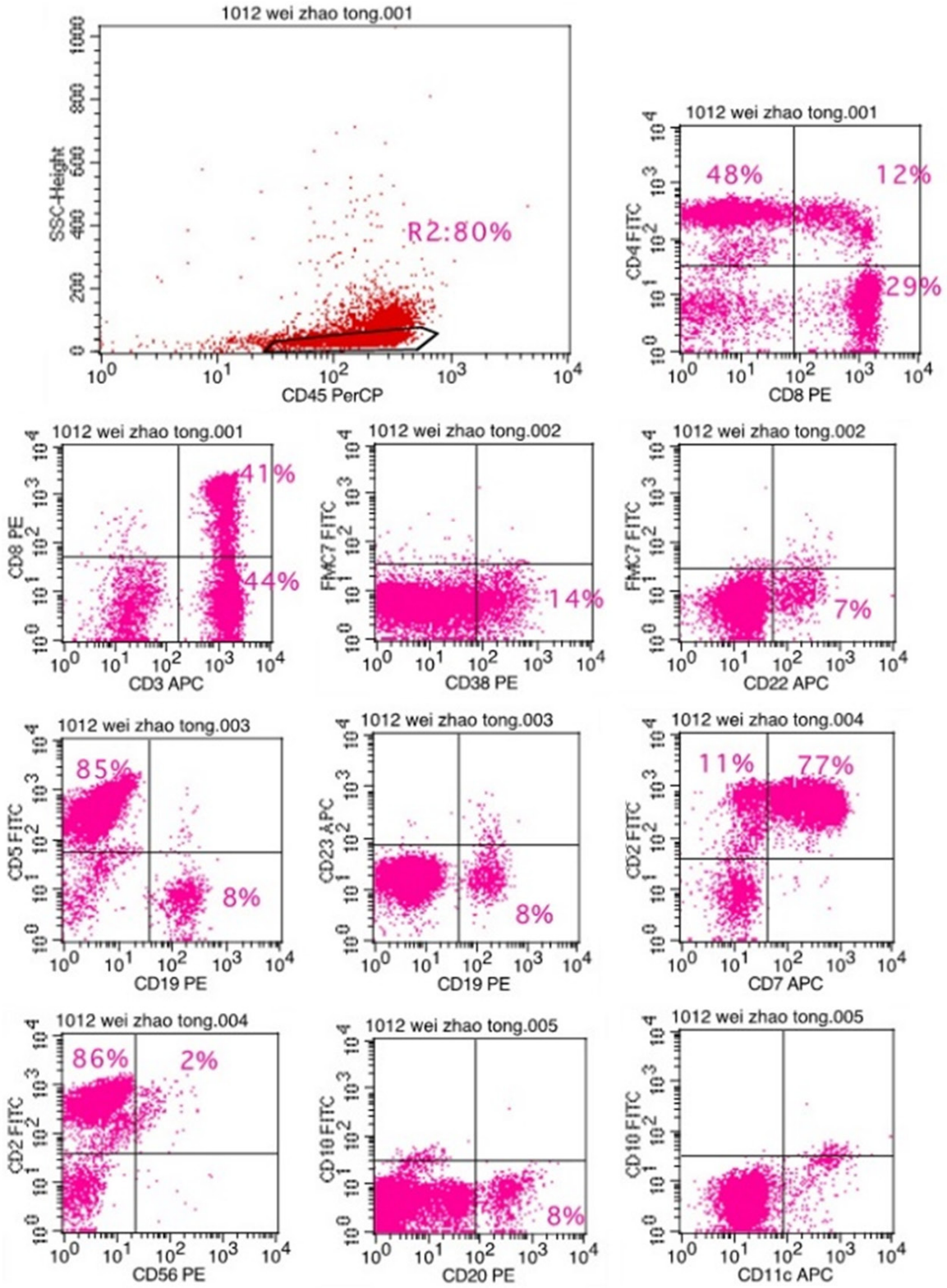

Figure 8. Flow cytometry of cells in pleural effusion. The figure showed that T lymphocytes account for about 80~90% of total cells in pleural effusion.

may well be more frequent by an incidence of 10 to 13% reported by Saif et al [13]. 5) Sweet Syndrome. Sweet syndrome is characterized by skin lesions with red or purple papules.

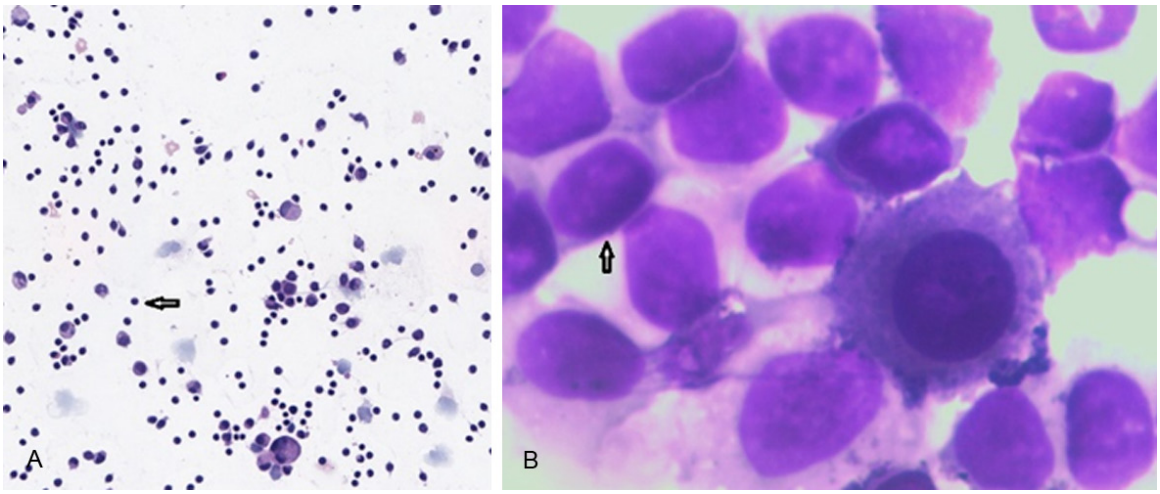

Figure 9. Exfoliative cells of pleural effusion. (A: Wright stain 40×, B: Wright Giemisa staining 100×). The cells in pleural effusion are mainly lymphocytes with several histocytes and mesothelial cells (the arrows: lymphocytes).

Table 2. Routine examinations of pleural fluid during three hospital stays

Variable	First visit June 2017	Second visit September 2017	Third visit May 2018
Color	Faint yellow	Faint yellow	Faint yellow
Characteristics	Transparent clear	Transparent clear	Transparent clear
Karyocyte count count (10^6/L)	337	946	156
Neutrophils (%)	5	3	2
Lymphocytes (%)	95	97	98
Protein qualitative	Negative	Negative	Weakly positive
LDH (U/L)	212	193	173
Total protein (g/L)	37.2	33.9	38.4
Albumin (g/L)	27.6	26.7	28.7
ADA (U/L)	13.1	11.6	11.8
Acid-fast bacilli	Negative	Negative	Negative

Extracutaneous manifestations are possible with pulmonary involvement. In a series of 79 patients with Sweet syndrome, Cohen reported 9% with MDS and 7% with CML in chronic or acceleration phase for 85% of the associated blood diseases [14]. 6) Hypereosinophilic Syndrome. Matsushima reported three cases of patients presenting this type of MDS with the same chromosomal abnormality der(1q;7p), bone marrow hypereosinophilia and pulmonary involvement [15]. In this case, the patient did not have the above comorbidity, and did not have 7) Pulmonary alveolar proteinosis or 8) Organizing pneumonia. On the other hand, Pulmonary Arterial Hypertension (PAH) is a common complication of myeloproliferative neoplasia, which is reported a poor prognosis [16]. The patient did have a PAH, but a sole PAH still could not well explain the intermittently asymmetric, lymphocyte dominated pleural effusion. In clinical, 9) Systemic Causes (thrombosis, liver dysfunction, cardiomyopathy, renal insufficiency, autoimmune conditions, volume overload) are common, which should be carefully excluded. As a result, the patient still was negative in systemic causes. Therefore, a definite pathogeny for pleural effusion was not found. Therefore, pleural effusion as a possible specific manifestation in MDS/MPN-RS-T was questioned. Although pleural effusions in hematologic malignancies do not necessarily portend poor prognosis [17], further prospective study is needed.

In terms of management, no formal guidelines for this disease exist [18] since it is extremely rare. Empirically, the management of MDS/MPN-RS-T is largely supportive. During his hos-

pitalization, supportive care like transfusion and drainage procedure for pleural effusion using indwelling pleural catheters was provided. Similar to lower risk MDS, the use of erythropoiesis stimulating agents (ESA) is instituted early on in patients with anemia. In the beginning, the patient did not use ESA for some personal reason even we strongly recommend when his serum EPO showing 67.4 mIu/ml. Aspirin therapy is reasonable in MDS/MPN-RS-T, especially in low risk patients with the presence of JAK2V617F [18, 19]. Afterwards, antiplatelet therapy (aspirin dynamically adjusted doses) was provided. Hydroxyurea is a common drug for cytoreductive therapy. But the value of cytoreductive therapy is debatable because it might exacerbate anemia. On the other hand, maybe patients should accept cytoreductive therapy when compelled by the presence of multiple risk factors for thrombosis [20]. Considering platelet count 1005~2200×10^9/L (normal range, 125-350×10^9/L) and other conditions, the Hu therapy was chosen and adjusted dynamically according to the CBC results. According to recent research, Lenalidomide showed a good clinical activity in this rare disorder [21]. However, economic reasons limited upfront use of it in this patient. Under our strong recommendation, he take the ESA therapy. Surprisingly, his Hb up to highest 90-110 g/L from the lowest 50-65 g/L. At the time of writing, the current state of the patient is stable and capable of living independently.

Overall, our patient's case illustrates that the asymmetric, lymphocyte dominated pleural effusion could possibly be an exceptionally clinical manifestations in patient with MDS/MPN-RS-T. Importantly, for super-aged patient, supportive care and the use of ESA can be successful especially when serum EPO <500 mIu/ml. Therapeutic options should be personalized to each case since there is not yet a standardized treatment of this disease.

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Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Bing Chen, Department of Hematology, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University, No 321, Zhongshan Road, Gulou District, Nanjing 210036, Jiangsu, China. Tel: +86 25 83105211; E-mail: chenb211@163.com; Dr. Yonggong Yang, Department of Hematology, Nanjing Drum Tower Hospital, School of Medicine, Nanjing University, No 321, Zhongshan Road, Gulou District, Nanjing 210036, Jiangsu, China. Tel: +86 25 83106666; E-mail: 915834491@qq.com

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