To the Editor: A 29-year-old Chinese woman was admitted for newly diagnosed acute promyelocytic leukemia (APL). Initial laboratory tests were as follows: white blood cell (WBC) count $1.68 \times 10^9/L$, hemoglobin 47 g/L, platelet count $35 \times 10^9/L$, and fibrinogen 0.81 g/L. There was no sign of pulmonary infection or serum biochemistry abnormality on admission. She was treated with all-transretinoic acid (ATRA) and arsenic trioxide (ATO) immediately. The coagulation indices were improved very soon, and there was no obvious bleeding. However, the patient developed rapidly progressing coughing with pinkish sputum and dyspnea accompanied by oliguria and facial edema since the 5th day of dual induction. Her WBC count limbed to $45.04 \times 10^9/L$ and creatinine level rose to 536 μmol/L. The diagnosis of ATRA syndrome was made, and we initiated intravenous dexamethasone 10 mg twice daily with daunorubicin 40 mg daily. Continuous renal dialysis was given to save her renal function. However, her respiratory status deteriorated with refractory hypoxia so that she was subsequently intubated. Massive bloody secretions were suctioned from her endotracheal tube. Computed tomography (CT) [Figure 1] before tracheal intubation showed bilateral diffuse interstitial infiltrates with poorly defined nodules, air-space consolidation, and ground-glass opacity. The possibility of diffuse pulmonary alveolar hemorrhage (DAH) secondary to ATRA was considered. Thus, we suspended ATRA immediately and continued with inflammatory-arresting dexamethasone combined with cytoreductive daunorubicin and ATO. Fortunately, with the above-mentioned therapy and respiratory support, her pulmonary lesion got absorbed. She was extubated successfully and achieved complete hematological remission.

Massive hemorrhage is a lethal complication in APL and disseminated intravascular coagulation (DIC) is its cause. Hence, it is the case with pulmonary hemorrhage in APL. However, in the era of differentiation induction therapy with ATRA and ATO, the risk of lethal hemorrhage secondary to DIC of APL including isolated lung bleeding has been significantly reduced. While ATRA syndrome is commonly encountered in APL’s induction course, DAH is a rare, often-neglected but life-threatening complication of ATRA syndrome. Pathogenesis of DAH in ATRA syndrome is yet to be elucidated. It is hypothesized that cytokine release by leukemic cells and leukocyte infiltration have contributed to DAH in ATRA syndrome.[1] Its morbidity was high in previous reports and many cases were only recognized by postmortem biopsy.[2]

Sometimes without pathology evidence, it is difficult to differentiate DAH from leukemic infiltration, pneumonia, and DIC-related pulmonary hemorrhage.[3] In our case, dyspnea with rapidly climbing WBC count and unexpected renal failure led us to the diagnosis of ATRA syndrome. Normalization of clotting test after induction and no signs of other organs bleeding have helped to rule out the possibility of DIC and DIC-related bleeding event. Moreover, CT images in this case highly support the diagnosis of DAH. DAH is often characterized by pathy zones of consolidation that rapidly coalesced to form air-space consolidation of both lungs in the background of ground-glass opacity and interlobular thickening which could be the early sign of pulmonary capillaritis of ATRA syndrome.[3] As shown in Figure 1, the CT image of this patient showed diffuse interstitial infiltrates along with patchy lesions characterized by poorly defined nodules, air-space consolidation, interlobular thickening, and ground-glass opacity.

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in this case, early recognition, instantaneous initiation of dexamethasone and daunorubicin, and adequate respiratory support if needed are the key of successful treatment and may help to improve its prognosis.

Declaration of patient consent
The authors certify that they have obtained appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

References
1. Raanani P, Segal E, Levi I, Bercowicz M, Berkenstat H, Avigdor A, et al. Diffuse alveolar hemorrhage in acute promyelocytic leukemia patients treated with ATRA – A manifestation of the basic disease or the treatment. Leuk Lymphoma 2000;37:605-10. doi: 10.3109/10428190009058513.
2. Miura Y, Kami M, Yamada M, Nagamatsu S, Matsumura T, Kodama Y, et al. Rapid diffuse alveolar hemorrhage associated with all-trans-retinoic acid and filgrastim. Am J Hematol 2008;83:683. doi: 10.1002/ajh.21194.
3. Jung JI, Choi JE, Hahn ST, Min CK, Kim CC, Park SH, et al. Radiologic features of all-trans-retinoic acid syndrome. AJR Am J Roentgenol 2002;178:475-80. doi: 10.2214/ajr.178.2.1780475.