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A young man with acute respiratory distress syndrome: eosinophilia is not always “benign”

TO THE EDITOR: Internists in intensive care units often encounter cases of acute respiratory distress syndrome (ARDS) that require mechanical ventilation. Such cases are difficult to manage and have a grim prognosis. Potential causes of ARDS include sepsis, trauma, pneumonia, infection, and uremia [1]. We describe a case of ARDS with associated eosinophilia that was diagnosed as a myeloid neoplasm with associated eosinophilia and *PDGFRA* gene rearrangement. Timely administration of imatinib mesylate

saved the patient's life without the need for invasive ventilation.

A 35-year-old man presented to our emergency department after coughing for 7 days and experiencing respiratory distress for 1 day. He had no history of fever, nasal discharge, chest pain, hemoptysis, hematuria, or passage of worms in his stool. He denied any atopy, recent travel, or exposure to pets, birds, cotton, dust, or metal fumes. His vital signs were as follows: blood pressure, 110/70 mm hg; pulse rate, 112 beats/minute; and respiratory rate, 30 breaths/minute. Remarkably, a general examination showed the presence of pallor and the use of the accessory muscles of respiration. There was no lymphadenopathy, cyanosis, clubbing, pedal edema, or palpable purpura, and the jugular venous pressure was not elevated. Bilateral rhonchi and crackles were audible on chest auscultation. The liver (4 cm in size) and spleen (5 cm in size) were palpable on abdomen examination. The results of a cardiovascular and neurological examination were unremarkable. A complete blood count revealed an hemoglobin level of 8.3 g/dL; white cell count of $27.6 \times 10^9/L$; a differential count of 39% polymorphs, 11% lymphocytes, 2% monocytes, and 48% eosinophils (absolute eosinophil count, $13.2 \times 10^9/L$); a platelet count of $420 \times 10^9/L$; and an erythrocyte sedimentation rate of 24 mm/hour. Serum levels of lactate dehydrogenase (LDH) and uric acid were 1,000 U/L and 565 $\mu\text{mol/L}$, respectively, and renal and liver function were normal. The results of an arterial blood gas analysis were consistent with type-1 respiratory failure: pH, 7.38; partial pressure of oxygen, 67 mm hg; partial pressure of carbon dioxide, 35.5 mmHg; and oxygen saturation, 85%.

A chest X-ray revealed bilateral fluffy alveolar opacities (Fig. 1A). Cardiac size and contour were normal. Contrast-enhanced computed tomography of the chest revealed symmetrical confluent airspace opacities in the bilateral central lung fields, suggestive of pulmonary edema (Fig. 2). Troponin I expression was negative, and pulmonary capillary wedge pressure (PCWP) measured by using a Swan-Ganz catheter was 5 mmHg. The serum procalcitonin level (0.3 $\mu\text{g/L}$) was normal, and blood cultures were sterile. *Leptospira*, *mycoplasma*, *legionella*, filariasis, and strongyloides stercoralis serology test results were negative, as were those for the legionella urine antigen, anti-nuclear antibody, and anti-neutrophil cytoplasmic antibody. Cysts/ova were not seen on stool examination. The serum immunoglobulin E level was 708 IU/mL, and nerve conduction was normal.

Owing to a possibility of Loeffler's pneumonia, diethylcarbamazine (300 mg in three divided doses) and a glucocorticoid (oral prednisone, 60 mg daily) were administered while awaiting a definitive diagnosis. The patient's symptoms did not improve and type-1 respiratory failure worsened; hence, bronchoscopy was performed. Bronchoalveolar lavage revealed an eosinophil-rich infiltrate, and histopathological examination of a transbronchial lung biopsy showed fibroblastic proliferation with formation of Masson bodies in the alveolar spaces (suggestive of organizing pneumonia),

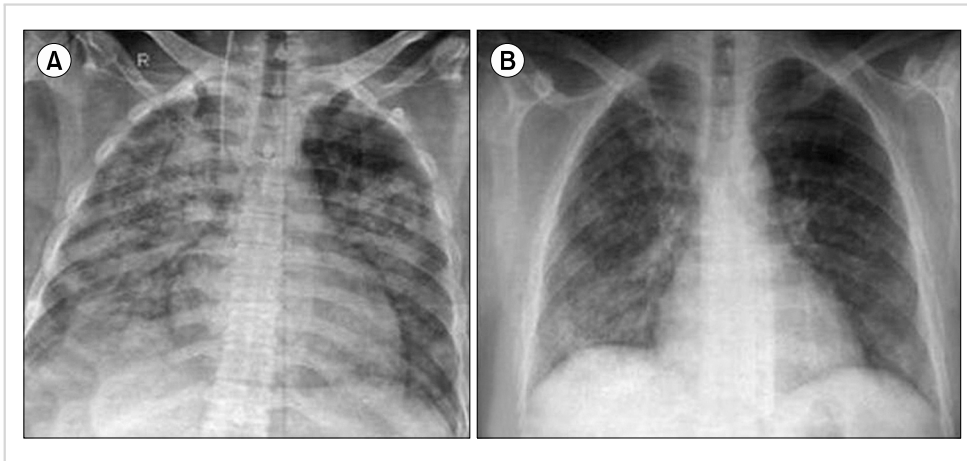


Fig. 1. (A) Chest X-ray (postero-anterior view) showing diffuse alveolar opacities with a normal cardiac shadow. (B) Chest X-ray 1 week after treatment with imatinib mesylate showing complete resolution of the infiltrates.

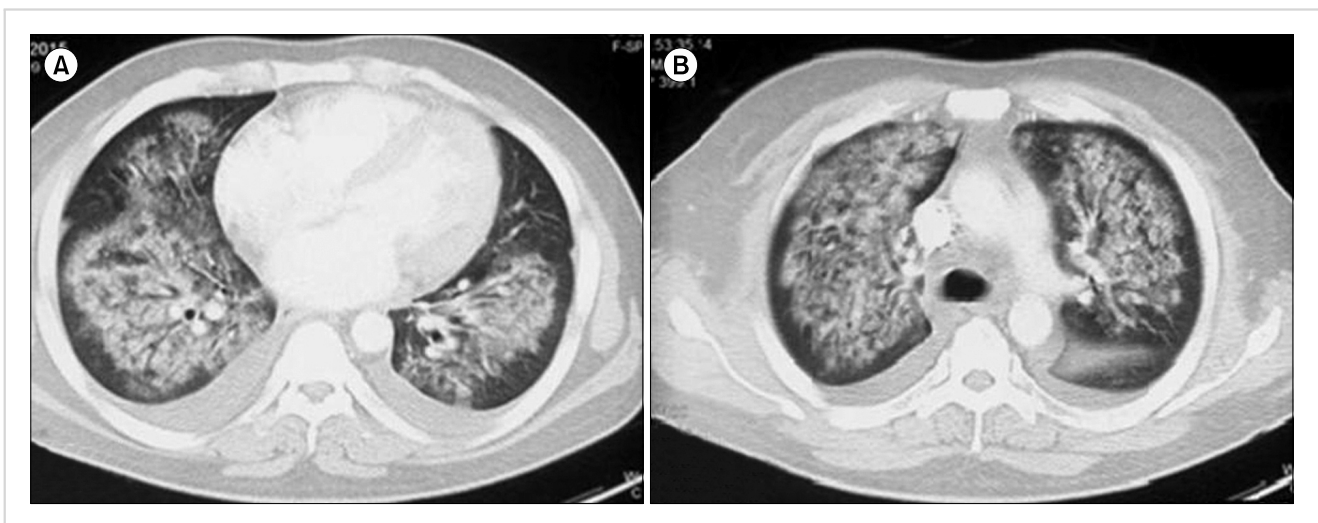


Fig. 2. (A, B) Computed tomography scans showing confluent symmetrical central airspace shadows indicating pulmonary edema.

along with the presence of eosinophils in the interstitial spaces (Fig. 3A). Bone marrow examination revealed granulocytic hyperplasia and a marked increase in the number of eosinophils without any blasts. *FIP1L1-PDGFR*A mRNA was detected in the peripheral blood via reverse transcriptase polymerase chain reaction, whereas *BCR-ABL1* mRNA was not.

The patient was diagnosed with a myeloid neoplasm associated with eosinophilia and *PDGFR*A gene rearrangement. Oral administration of imatinib (100 mg daily) led to a marked clinical, radiological, and hematological improvement within 1 week (Fig. 1B) and complete hematological remission (CHR) at 2 weeks (normalization of peripheral blood counts and no splenomegaly). He was subsequently discharged in stable condition. He is still undergoing regular follow-ups at the time of this write-up.

Eosinophilia is a relatively common finding in clinical practice and is often overlooked in the face of other clinical and biochemical features. Hypereosinophilic syndrome (HES) was initially defined by Chusid *et al.* [2] as (a) eosino-

philia ($>1.5 \times 10^9/L$ eosinophils) for more than 6 months, (b) exclusion of secondary causes of eosinophilia such as drugs, allergies, and parasites, and (c) evidence of end organ damage. The first requirement was later removed to allow diagnosis of HES before permanent organ damage [3]. Owing to the recognition of recurrent cytogenetic and molecular abnormalities in patients with hypereosinophilia and because sustained eosinophilia can lead to end organ damage regardless of cause, eosinophilic disorders were reclassified by the World Health Organization in 2008 as (a) myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities in the *PDGFR*A, *PDGFR*B, and *FGFR*1 genes, (b) chronic eosinophilia not otherwise specified, and (c) idiopathic HES. The term “HES” is now used to describe end organ damage secondary to hypereosinophilia of any etiology [4].

HES most commonly affects the hematological system (100%), cardiovascular system (58%), skin (56%), nervous system (54%), and pulmonary system (49%) [5]. Pulmonary involvement is a direct result of eosinophil-mediated damage

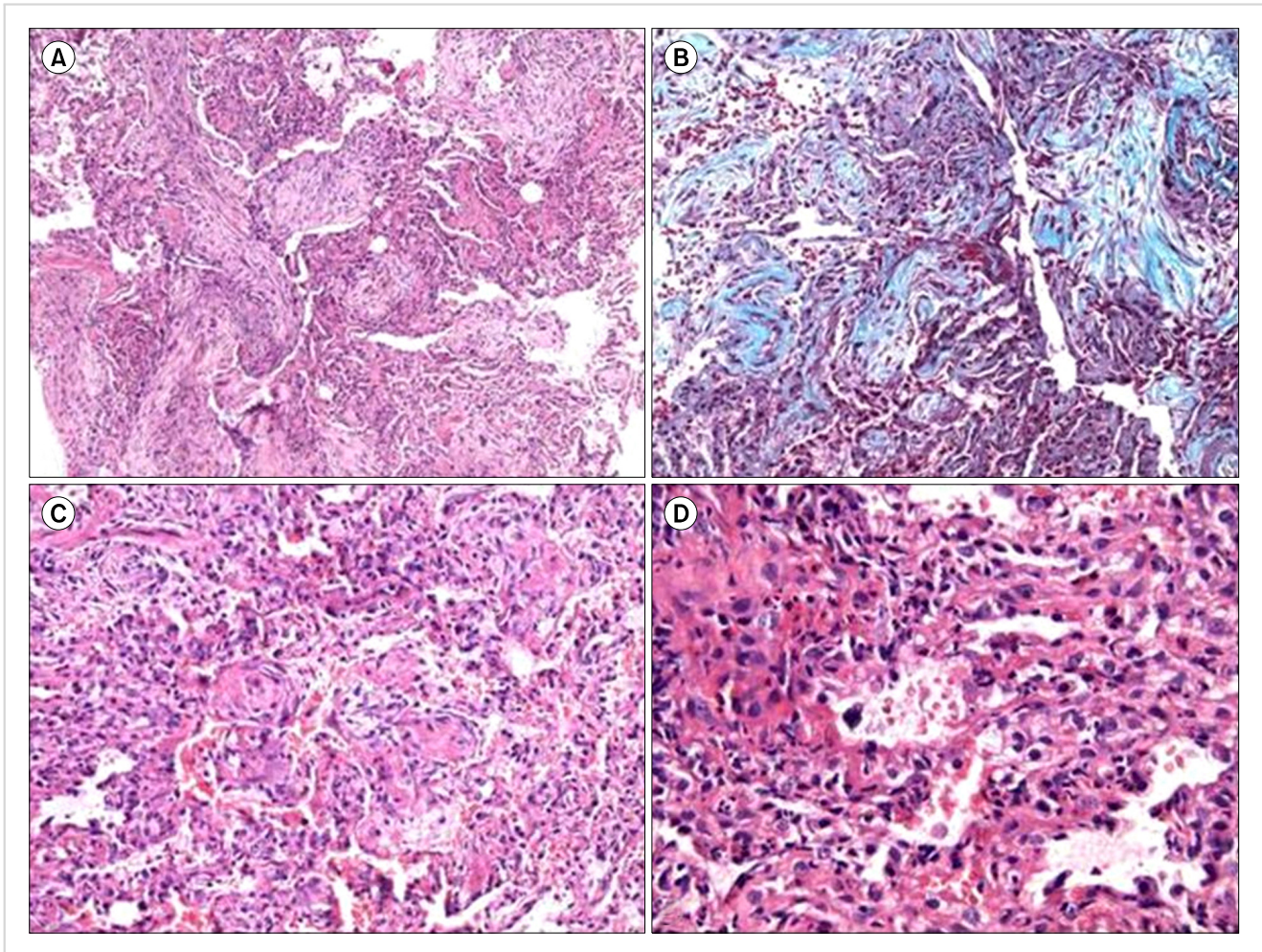


Fig. 3. Photomicrographs showing (A) intra-alveolar Masson bodies indicating an organizing pneumonia pattern (hematoxylin and eosin, $\times 200$), (B) Masson bodies (Masson's trichrome stain, $\times 200$), (C) a few alveoli with fibrin balls (hematoxylin and eosin, $\times 200$), and (D) an interstitial eosinophilic infiltrate (hematoxylin and eosin, $\times 400$).

or an indirect result of cardiac failure, pulmonary embolism, drug-related injuries, infection, or asthma [5, 6]. The clinical presentation includes nocturnal coughing, wheezing, productive sputum, and dyspnea. Radiographic pulmonary abnormalities (14–28% of cases) include nodules, interlobular septal thickening, ground-glass opacities, pleural effusion, focal or diffuse infiltrates, atelectasis, fibrosis, and on rare occasions, hilar adenopathy and pulmonary hypertension [6]. Occurrence of ARDS in HES is extremely rare, with only a few case reports [6, 7]. In a study by Dulohery *et al.* [6] of 49 patients with HES, symptomatic pulmonary involvement, radiographic abnormalities (parenchymal infiltrates, pleural effusion, lymphadenopathy, and emboli), and asthma were observed in 63%, 43%, and 27% of the patients, respectively; none of the cases involved ARDS. The most commonly reported radiographic findings for HES are ground glass opacities and patchy consolidation.

Imatinib (100–400 mg daily) is the standard treatment for myeloid/lymphoid neoplasms with *PDGFRA* gene rearrangements, and almost all patients with this disease ach-

ieve CHR and a 3-log reduction in *PDGFRA* transcript levels within 1 month and 1 year of therapy, respectively. Primary and acquired imatinib resistance is unusual. Relapses after imatinib discontinuation have been documented, but molecular remission can be successfully achieved following imatinib re-initiation [8]. The absence of troponin-I expression and a normal PCWP ruled out cardiogenic pulmonary edema secondary to heart involvement in our case.

The present case highlights two important points: HES is an important reversible etiology of ARDS, and eosinophilia in the setting of ARDS should never be overlooked. The presence of organomegaly and an elevated LDH level may provide early clues as to the underlying myeloproliferative process. *FIP1L1-PDGFR*A transcripts must be identified as early as possible in HES cases, as treatment with imatinib may aid patients without the need for mechanical ventilation.

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Does the c.-273T>C variant in the upstream region of the *HBB* gene cause a thalassemia phenotype?

TO THE EDITOR: Beta thalassemia is a hereditary disease that results from mutations in the *HBB* gene, leading to genetic defects in the production of beta-globin chains [1, 2]. *HBB* encodes beta-globin, a subunit of hemoglobin. In

adults, hemoglobin is normally made up of four protein subunits, including two subunits of beta-globin and two subunits of alpha-globin, with the latter produced from *HBA*. Mutations in *HBB* can result in either beta-plus (B⁺) thalassemia that is responsible for a less severe form of thalassemia (caused by a decrease in beta-globin production) or beta-zero (B⁰) thalassemia that is the severe type of the disease (caused by a total lack of beta-globin) [3-8].

The mutations usually include missense or nonsense types, but other types, such as deletions of the beta-globin gene and surrounding regions, also have been identified in thalassemia patients. According to the Human Gene Mutation Database (HGMD), currently, 835 disease-causing mutations have been found in *HBB*, including 404 missense/nonsense, 118 small deletions, 97 gross deletions, 73 regulatory, 53 splicing, 44 small insertions, 21 complex rearrangements, 19 small indels, and six gross insertions (<http://www.hgmd.cf.ac.uk/ac/gene.php?gene=HBB>).

In addition, different studies have reported variants with unknown significance in the 5' region, near the splice sites, and in the 3' area of *HBB*, including c.-273T>C (upstream of the gene) [9]; until date, there have been no comprehensive data regarding its role in the phenotype of thalassemia. The goal of this study was to clarify the significance of this variant using segregation and bioinformatics analysis. Thus, from our large number of samples recruited from cases of minor thalassemia, we collected data regarding their laboratories and genetic studies. All patients provided informed consent before undergoing molecular testing for *HBB* and *HBA* mutation analysis. This study was approved by the institutional review board of the Comprehensive Medical Genetics Center, Shiraz University of Medical Sciences (Approval No. 95.113.). Genomic DNA was extracted from the peripheral blood lymphocytes of these samples using DNA Extraction Kits (Yekta Tajhiz, Iran) according to the manufacturer's instructions, and the DNA concentration was measured by NanoDrop (ND1000, USA) and stored at -20°C until use.

Sequences covering all coding and important non-coding regions of *HBB* and *HBA 1* and *2* genes were amplified by PCR. The total volume used for the PCR was 50 μ L including 1 μ L of each primer (20 pmol/ μ L), 2 μ L DNA template (50-200 ng), 25 μ L TEMPase Hot Start 2x Master Mix Blue (Ampicon, A290806), and 21 μ L dH₂O. The PCR reactions were carried out according to Ampicon TEMPase Hot Start protocol and programs. Ten microliters of the PCR products were visualized on 2% agarose gel containing SYBR Safe. For mutation analysis for *HBA 1* and *2* genes, ViennaLab StripAssays was used to locate all important deletions that were not detected by standard PCR.

From 200 samples of different types of suspected minor thalassemia, we found 12 cases with c.-273T>C. It is worth noting that one of the cases had this variant in a homozygous pattern and another of the cases with c.-273T>C had a pathogenic mutation. All heterozygous cases for c.-273T>C (cases 1-10) and also that of the homozygous form, including