Progressive Dyspnea in a Common Variable Immune Deficiency Patient: Please Sit for the Diagnosis

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Common variable immunodeficiency (CVID) is a heterogeneous primary immune deficiency disorder characterized mainly by defective B lymphocyte differentiation, leading to hypogammaglobinemia and defective antibody production. It is often combined with cellular immune defects. A minority of patients present during childhood and adolescence. Infections are most often sinopulmonary but can affect any system. The noninfectious complications include progressive lung disease, autoimmunity, gastrointestinal inflammatory disease, liver disease, granulomatous disease, lymphoid hyperplasia and infiltrative disease, and the development of lymphoma and other cancers. In addition to recurrent infections and bronchiectasis, patients may develop chronic interstitial lung disease, granulomatous lung disease, lymphoma, and pulmonary hypertension.

We present a complex young adult patient with CVID who developed progressive dyspnea and hypoxemia. The possibility of hepatopulmonary syndrome was considered and repeated bubbles echocardiographic studies were performed and reported as normal.

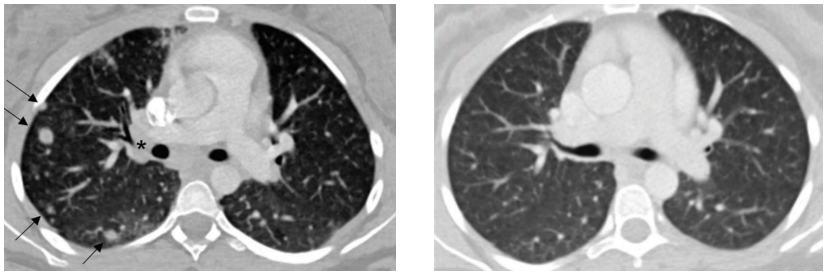
Only when contrast echocardiography was performed while sitting was a right-to-left shunt revealed and hepatopulmonary syndrome (HPS) diagnosed. This case illustrates the significance of performing bubble echocardiography in the upright or seated position for HPS diagnosis.

Figure 1. Axial chest CT with intravenous contrast injection at the level of the lower lobes, resolved completely 5 years later

CT = computed tomography

[A] A chest CT scan with multiple round nodules (black arrows) of different sizes in the right lower lobe and hilar lymphadenopathy (*)

[B] Five years later



PATIENT DESCRIPTION

A 24-year-old female presented at the age of 13 years with autoimmune hemolytic anemia (AIHA), lymphadenopathy, and hepatosplenomegaly without respiratory symptoms. Following an abdominal computed tomography (CT), which showed peripheral nodules at the base of the lungs, a chest CT was performed revealing bilateral pulmonary nodules and sub-carinal lymphadenopathy. Cardiac echocardiography, lung volumes, spirometry and diffusion capacity were normal. Laboratory tests revealed low immunoglobulin levels and partial response to vaccines. Lymph node biopsy showed reactive inflammation with non-caseating granulomas. Based on the combination of autoimmunity and hypogammaglobulinemia, the diagnosis of CVID was established. She responded well to pulse steroids and monthly intravenous gamma globulin (IVIG).

At the age of 15 years she developed a daily productive cough. Repeat chest CT revealed bilateral nodules and ground glass opacities. Lung biopsy revealed granulomatous lymphocytic interstitial lung disease (GLILD).

At the age of 20 years, she had mildly elevated liver transaminase levels, marginal levels of albumin, and prolonged partial thromboplastin time (PTT) with normal international normalizing ratio. Liver ultrasonography was normal. Hepatitis workup was negative. Liver biopsy showed mild

nonspecific inflammation without fibrosis. Steroid treatment resulted in normalization of transaminases and PTT.

She continued to periodically present with multiple relapsing and remitting autoimmune manifestations. Infections were scarce. She was treated with rituximab, steroids, and azathioprine, usually with good clinical response.

During the next 4 years, she presented with progressive lung disease. Pulmonary function tests gradually deteriorated. Her forced expiratory volume (FEV1) decreased from 79% to 55%, forced vital capacity (FVC) decreased from 79% to 62%, FEV1/FVC from 87% to 78%, and total lung capacity from 83% to 75%. Diffusion capacity was decreased to 49%. At the age of 22 years, she started to become hypoxemic at rest, with saturation levels approximately 92%, while developing digital clubbing. Skin spider angiomas evolved with mildly echogenic liver on ultrasound. Bubble echocardiography was performed repeatedly with normal cardiac anatomy and no evidence of pulmonary hypertension or right-to-left shunt. There was no improvement with antibiotic courses; hence, the hypoxemia was attributed to GLILD. She was treated with systemic steroids and rituximab. Following the third dose of rituximab, she developed multiple brain abscesses, with full resolution after a few months of antibiotics.

Her dyspnea worsened, and her oxygen saturation dropped from 92% to 75% and increased to 90% after high flow oxygen administration. She remained bedridden. Repeated bubble echocardiographic assessments were negative. Lung transplant and/or bone marrow transplantation were considered.

A repeat chest CT showed improvement in her lung findings [Figure 1] while her clinical state was deteriorating.

Due to the deteriorating hypoxemia, even with radiographic improvement in her chronic lung disease, a repeat contrast echocardiography while sitting rather than supine was requested. This echocardiogram demonstrated an intrapulmonary shunt with bubbles seen in the left ventricle during the fourth heartbeats. Blood gasses test while seated revealed an increased alveolar arterial oxygen gradient (A-a O_2) of 72 mmHg. These findings, in addition to clinical and radiological signs of liver disease, were consistent with the diagnosis of hepatopulmonary syndrome.

A repeated liver biopsy showed severe small droplet macrovesicular steatosis with lobular lymphocytic inflammation and focal ballooning. Liver and bone marrow transplants (BMT) were considered.

COMMENT

The clinical condition of a 24-year-old female with CVID complicated by mild liver disease was deteriorating, with worsening hypoxemia, while radiographic pulmonary findings based on CT were improving. This discordance warranted consideration of a different diagnosis. The increased hypoxemia raised the suspicion of HPS. The diagnosis of HPS was only confirmed after performing echocardiogram bubble while sitting.

Hepatopulmonary syndrome is characterized by the presence of intrapulmonary vascular dilatations (IPVD) in patients with cirrhotic and non-cirrhotic liver disease. The classic symptoms of HPS are platypnea with orthodeoxia. Extrapulmonary complications include cerebral abscesses or hemorrhages and polycythemia.

The mechanisms of hypoxemia include V/Q mismatch, alveolar capillary diffusion limitation, and arteriovenous fistulae development [1]. Standing up results in a gravitational redistribution of pulmonary blood flow to the lower lung zones where the dilated vessels and fistulae are common, worsening the hypoxemia in HPS patients.

Diagnosing HPS in a patient with liver disease requires oxygen partial pressure < 80 mmHg or an (A-a O_2) ≥ 15 mmHg taken from a seated patient, and evidence of IPVD (on contrast echocardiography or radioactive lung-perfusion scanning) [1].

In a recent review of platypnea-orthodeoxia syndrome (POS), Agrawal and colleagues [2] found that an intracardiac communication between the two atria was the most common cause of POS in 208 of 239 cases (87%) described in the literature. Other causes were extracardiac shunts including HPS and other miscellaneous disorders. To obtain the highest sensitivity for diagnosing intracardiac shunts, it is recommended to perform contrast echocardiography in the supine in the upright position. To the best of our knowledge there are no guidelines to perform upright contrast echocardiography for suspected extracardiac shunts.

Contrast echocardiography is considered the modality of choice for diagnosing of IPVD and HPS. While the transfer of bubbles from right to left heart chambers in extracardiac shunts takes place between the third and sixth heartbeats, in intracardiac shunts it occurs earlier, between the first and third beats.

Our patient underwent four contrast echocardiographic studies while supine, which showed normal cardiac anatomy without evidence of intracardiac or extracardiac shunt. Only when the contrast echocardiography was performed while sitting up were bubbles seen in the left heart chambers during the fourth heartbeats suggesting an extracardiac shunt. We suspect that the gravitational redistribution of pulmonary blood flow while our patient was upright aggravated the blood flow through the arteriovenous fistulae and revealed the diagnosis.

Lenci and colleagues [3] performed contrast echocardiography in the standing and supine positions in 13 cirrhotic patients and showed that the standing position can increase both the number and the size of shunts compared with supine injection. Boryczka and co-authors [4] showed a higher proportion of intrapulmonary blood shunting in erect versus supine patients using albumin scintigraphy in liver disease.

Early identification of HPS is important due to the progressive nature of the syndrome. The only treatment to improve

survival rates for patients with HPS is liver transplant [5]. Our patient described raised a complex therapeutic dilemma. Theoretically, a successful BMT could reverse the immunological defect while a liver transplant could reverse the hepatopulmonary syndrome. Both procedures carry high risk in a hypoxic patient with immune deficiency. The delayed confirmation of HPS in our patient may have further aggravated the outcome. Our case supports the recommendation of contrast echocardiography in the upright position in patients with unexplained hypoxia and a clinical suspicion of HPS.

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References

1. Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome--a liver-induced lung vascular disorder. *N Engl J Med* 2008; 358: 2378-87.
2. Agrawal A, Palkar A, Talwar A. The multiple dimensions of Platypnea-Orthodeoxia syndrome: a review. *Respir Med* 2017; 129: 31-8.
3. Lenci I, Alvior A, Manzia TM, Toti L, Neuberger J, Steeds R. Saline contrast echocardiography in patients with hepatopulmonary syndrome awaiting liver transplantation. *J Am Soc Echocardiogr* 2009; 22: 89-94.
4. Boryczka G, Hartleb M, Rudzki K, Janik MA. Influence of an upright body position on the size of intrapulmonary blood shunts in patients with advanced liver cirrhosis. *J Physiol Pharmacol* 2015; 66: 855-61.
5. Iyer VN, Swanson KL, Cartin-Ceba R, et al. Hepatopulmonary syndrome: favorable outcomes in the MELD exception era. *Hepatology* 2013; 57: 2427-35.

A man has to live with himself, and he should see to it that he always has good company.
Charles Evans Hughes (1862–1948), American statesman, politician, Cornell Law School Professor, and jurist

There is no remedy so easy as books, which if they do not give cheerfulness, at least restore quiet to the most troubled mind.
Lady Mary Wortley Montagu (1689–1762), English aristocrat, writer, and poet

Capsule

One-click cancer cell destruction

Efficient targeting of cancer cells is an important goal for developing less generally toxic treatments. The enzyme aldehyde dehydrogenase 1A1 (ALDH1A1) is overexpressed within breast cancer cells but itself is not a direct target for treatment. To detect and selectively kill cancer stem-like cells, **Bo** et al. designed an azido sugar-like molecule that serves as a substate for ALDH1A1. The designed substrate causes a chemical tag to be linked to glycoproteins on the cell surface, signaling the presence of ALDH1A1. The surface azide tag is recognized in animals treated with dibenzocyclooctyne (used in *click* chemistry) conjugated to a toxin. The toxin kills cells and makes tumors regress. Small azido sugars and DBCO toxins have better tissue penetration than larger molecules such as antibodies.

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Capsule

Targeting RyR2 to prevent chemobrain

Cancer survivors often experience cognitive impairments after chemotherapy, a side effect commonly known as *chemo brain*. **Liu** et al. treated mice with breast cancer and wild-type mice with one of two chemotherapeutic regimens, doxorubicin or methotrexate and 5-fluorouricil, to investigate the role of ryanodine receptor type 2 (RyR2) in chemo brain. The authors identified chemotherapy-induced posttranslational modifications and increased calcium leakiness of RyR2. Treatment with a ryanodine receptor calcium release channel stabilizer (S107) prevented chemotherapy-induced RyR2 leakiness and ameliorated cognitive deficits in these breast cancer mice. The authors found similar chemotherapy-induced RyR2 modifications and cognitive deficits in cancer-free mice, indicating that chemotherapy without cancer was sufficient to induce chemo brain in mice. These preclinical results suggest that targeting RyR2 might be a promising target to prevent this unwanted side effect of chemotherapy.

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