Case record

An unusual case of pulmonary hypertension in a young male

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Presentation and history

Dr. Carlo Rostagno: A 31-year-old man, affected in childhood by atopic bronchial asthma, in November 2002 began to complain of dyspepsia, abdominal tenderness and distension. In February 2003 atraumatic fracture of tenth left rib. In March 2003 laboratory exams prescribed for the recurrence of abdominal pain showed only a mild normochromic anaemia and thrombocytopenia. No further clinical investigation was performed.

He came to our observation at the end of March 2003. At physical examination the patient was pale, tachypnoic (24 breaths/min), tachycardic (104 b/min) with a presystolic gallop rhythm. The jugular veins were distended with epatojugular reflux. Liver and spleen were both enlarged and ascites was detectable. Right basal percussory hypophonesis was found at chest examination. Electrocardiogram was not remarkable except for sinus tachycardia (Fig. 1). Echocardiogram showed a normal sized left ventricle with paradox motion of the interventricular septum. The right ventricle was dilated (34 mm) as the main pulmonary artery. A high-velocity tricuspid regurgitant jet was detected with an estimated systolic pulmonary pressure of 80 mmHg (Figs. 2 and 3). The inferior vena cava was dilated (30 mm) without breathing-related changes.

Preliminary diagnosis

Dr. Rostagno: Clinical data suggest the diagnosis of severe pulmonary hypertension (PH) with signs of congestive heart failure in a young male without history of congenital heart disease, respiratory insufficiency (he suffered from mild atopic bronchial asthma in childhood) or assumption of anorexigens or other drugs associated with PH. In the absence of clear predisposing factors, clinical work-up was started to rule out or confirm the hypothesis of idiopathic PH.

Discussion of diagnosis

Dr. Domenico Prisco: The history in this case is really poor, the patient reported only few episodes of atopic bronchial asthma in childhood. The first clinical manifestations of the disease may be dated back to November 2002 when he began to complain of abdominal tenderness, probably related to liver congestion. The patient had no known congenital heart disease and physical examination of the heart was negligible except for the presence of presystolic gallop rhythm. Echocardiography showed indirect signs of severe PH with a high-velocity tricuspid regurgitation, enlargement of right cardiac chambers and paradox motion of the interventricular septum.

PH comprises a group of diseases characterised by an increase in pulmonary vascular resistance leading to right ventricular failure. PH can be classified into four main categories: pulmonary arterial hypertension (PAH), pulmonary venous hypertension, PH associated with hypoxaemia, and PH due to chronic thrombotic or embolic disease. Classification of PH according to the World Health Organisation is reported in Table 1. History and chest X-ray allow ruling out PH secondary to lung disease or hypoxemia. Echocardiogram did not show any significant morphologic abnormalities, thus suggesting a relatively acute increase of pulmonary pressure. Moreover, pulmonary artery pressure was significantly higher than usually found in young patients with pretricuspid left-to-right shunt. Despite the low probability, we performed a transoesophageal echocardiography, which did not disclose atrial septal defects nor anomalous return of pulmonary veins (Fig. 4). Cardiac magnetic resonance imaging confirmed right ventricular dilatation with severe tricuspid regurgitation without evidence of left-to-right shunt.

Idiopathic PAH occurs in women more often than men (2:1) with a mean age at diagnosis of 36 years, and is usually fatal within 3 years if untreated. Modern treatment has markedly improved physical function and has extended survival, and the 5-year mortality rate is 50%. Approximately 10% of patients diagnosed with PAH...
without a demonstrable cause have a family history of the disease and are referred to as having familial PAH, whereas the remainder is classified as having idiopathic PAH. As the patient’s clinical conditions showed a further worsening, 10 days after the first examination he was hospitalized to complete clinical evaluation.

**Further investigations, diagnosis and treatment**

*Dr. Rostagno:* On hospital admission clinical conditions were stable, physical examination did not show any additional findings. Laboratory examination showed a normochromic anaemia (haemoglobin 9.7 g/dl, mean corpuscular volume 91.6 µm³), thrombocytopenia (122 × 10⁹/l) and an increased plasma protein concentration (9.6 g/dl) with hypergammaglobulinaemia (40.2%). Immunoelectrophoresis revealed an IgG monoclonal peak (IgG 3290 mg/dl) (Fig. 5) associated with Bence-Jones λ proteinuria (1694 mg/24 h), B₂ microglobulin (7.8 mg/dl), serum calcium (10.7 mEq/l) and uric acid (10 mg/dl) were increased. The other laboratory tests were in the normal range. Skeletal X-ray showed multiple advanced lytic bone lesions.

*Dr. Stefania Ciolli:* Results from laboratory examination and X-ray are highly suggestive of a severe plasma cell
proliferative disorder and bone marrow examination is mandatory to confirm the diagnosis. However, we still have to understand if a relationship may exist between PH and plasma cell disease or if the two conditions are not related each other.

Bone marrow biopsy revealed 80% clonal plasma cells (CD20+, CD38+, κ, λ+, clgG+). According to the Durie and Salmon staging system, a diagnosis of multiple myeloma (MM) stage IIa was made. Fluorescence in situ hybridisation on bone marrow plasma cells did not detect a del (13)(q14) deletion. Ploidy and cell cycle status were assessed by flow-cytometry employing propidium iodide; plasma cells had a high labelling index (3.64%) and 99% of them were aneuploid with less than normal DNA contents. Biopsy of periumbilical fat was diagnostic for amyloidosis. Although an increase in pulmonary artery pressure is not unusual in patients with restrictive heart disease due to amyloidosis secondary to plasma cell diseases, precapillary PH has been reported as a rare complication of MM. The relatively sudden increase of pulmonary vascular resistance and the discovery of a neoplastic disease compel to rule out pulmonary thromboembolism as a cause for PH.

Dr. Prisco: Deep venous thrombosis and pulmonary embolism are not a rare complication of neoplastic diseases leading sometimes to severe thromboembolic PH. Clinical presentation of chronic thromboembolic hypertension follows two main patterns: the first include progressive dyspnoea on exertion, haemoptysis, and/or signs of right heart dysfunction including fatigue, palpitations, syncope, or oedema after a single episode or recurrent episodes of pulmonary embolism. The development of clinical signs may last from a few months to many years. However, three fourths of patients have no history of acute pulmonary embolism. The clinical course is often indistinguishable from other forms of severe PH, especially idiopathic PAH. Imaging technologies including

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**Table 1. Clinical classification of pulmonary hypertension according to the World Health Organisation.**

1. Pulmonary hypertension
   a) Idiopathic
   b) Familial
   c) Associated with connective tissue, systemic to pulmonary shunts, portal hypertension, HIV infection, drugs and toxins, other
   d) Associated with significant venous or capillary involvement, pulmonary veno-occlusive disease, pulmonary capillary haemangiomatosis
   e) Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension associated with left heart disease
   a) Left-sided atrial or ventricular heart disease
   b) Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung disease and/or hypoxia

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   a) Thromboembolic obstruction of proximal pulmonary arteries
   b) Thromboembolic obstruction of distal pulmonary arteries
   c) Non thrombotic pulmonary embolism (tumour, parasites, foreign material)

5. Miscellaneous

   HIV, human immunodeficiency virus.
and the lung spiral CT were negative for pulmonary embolisation. According to guidelines on diagnosis and treatment of PH of the European Society of Cardiology, a normal ventilation-perfusion scintigram practically rules out the presence of chronic thromboembolic hypertension. Abdomen ultrasonography and CT confirmed severe liver enlargement with distended inferior vena cava and sovrahepatic veins and ascites in the absence of focal lesions.

Dr. Ciolli: Several cases of PH were described in patients suffering from a rare syndrome associated with poly-neuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS)12-14. One fourth of patients with POEMS followed up during a 10-year period developed PH15. Abnormal release of vasoactive cytokines has been implicated in the pathogenesis of the disease16-18. In our patient, diagnosis of POEMS syndrome was hypothesised; however, he did not show endocrinological symptoms and neuro-physiological studies were negative. Vincristine, adryamicin, dexamethasone (VAD) (vincristine 0.4 mg plus adriamycin 9 mg/m² and dexamethasone 40 mg i.v. days 1-4, 9-12, 17-20) for treatment of MM was started. After one chemotherapy cycle (29 April) clinical conditions significantly improved, haemoglobin was increased (11.8 g/dl), platelet count was normal, IgG monoclonal protein (IgG 1170 mg/dl), B2 microglobulin (3.2 mg/dl) and Bence-Jones proteinuria (340 mg/24 h) were significantly decreased.

Dr. Rostagno: Right heart catheterisation performed 20 days after starting treatment showed a significant decrease of pulmonary artery pressure (39/22 mmHg, mean 32

ventilation-perfusion scanning, computed tomography (CT), magnetic resonance imaging, and pulmonary angiography are a fundamental part of the diagnostic work-up of patients with suspected chronic thromboembolic hypertension. An hypercoagulable state has been described in patients with MM; recently Zangari et al.9 showed a resistance to activated protein C in absence of factor V Leiden mutation in patients with myeloma. This resistance is associated with a 4-fold increase of deep venous thrombosis and pulmonary embolism. Interference of immunoglobulins with fibrin structure, procoagulant antibodies, endothelial damage due to the effects of inflammatory cytokines released by neoplastic cells are additional procoagulant factors in MM.10

Finally, hyperviscosity associated with elevated serum protein concentration may increase pulmonary vascular impedance. However, leg vein thrombosis was ruled out by Doppler examination and perfusion lung scintigraphy and the lung spiral CT were negative for pulmonary embolisation. According to guidelines on diagnosis and treatment of PH of the European Society of Cardiology, a normal ventilation-perfusion scintigram practically rules out the presence of chronic thromboembolic hypertension. Abdomen ultrasonography and CT confirmed severe liver enlargement with distended inferior vena cava and sovrahepatic veins and ascites in the absence of focal lesions.

Figure 4. Transoesophageal echocardiograms showing intact atrial septum and absence of anomalous venous return.

Figure 5. Serum immunoelectrophoresis showing a sharp monoclonal peak in the γ-globulin region.
mmHg). Cardiac index was normal (4.5 l/min/m²). Moreover, echocardiography showed a decrease of right ventricular size, trivial tricuspid regurgitation and disappearance of paradox motion of the interventricular septum. The size of the inferior vena cava was within normal limits with recovery of respiratory related changes. Left ventricular function was normal (ejection fraction > 60%), without abnormalities of diastolic function. Abdomen ultrasonography was negative. Chest X-ray was normal. The patient was discharged in the first days of May 2003 in good clinical conditions and VAD cycles were administered on an outpatient basis.

**Dr. Ciolli:** At the end of August 2003, after the fourth VAD cycle, peripheral blood counts (white blood cells 6.67 × 10⁹/l, haemoglobin 14.6 g/dl, platelets 336 × 10⁹/l) were normal, Bence-Jones proteinuria was negative and total plasma proteins were normal (6.9 g/dl), but a monoclonal component persisted (IgG 987 mg/dl). A bone marrow biopsy showed 30% of plasma cells. According to the European Bone Marrow Transplantation criteria, the patient was considered as a partial responder. Thus he received two additional cycles of melphalan 30 mg/m² with a significant decrease of bone marrow plasma cells infiltration (from 30 to 8%). Cardiological examination did not disclose any significant abnormalities, in particular the size of right heart chambers was normal and tricuspid regurgitation no more appreciable. Pulmonary acceleration time was normal (120 ms).

Since he did not have an human leucocyte antigen identical sibling donor, a stem cell mobilisation program with cyclophosphamide 3 g/m² plus granulocyte-colony stimulation factor 5 µg/kg and a double autologous peripheral blood stem cell transplant with melphalan 200 mg/m² were scheduled. Peripheral blood stem cell collection was successful with 2.75 × 10⁶/kg CD34+ cells. The first peripheral blood stem cell transplantation was performed at the end of December 2003 and the second one on April 2004. At discharge, the patient had achieved the MM complete remission; physical examination and laboratory tests were normal, except for a drug-induced cytopenia.

At 22-month follow-up the disease was still in clinical remission and the patient could resume his work and physical activities. Serial echocardiographic examinations confirmed a normal sized left ventricle (ejection fraction > 60%), no more than trivial tricuspid regurgitation and normal sized right heart chambers (Fig. 6).

**Discussion**

**Dr. Rostagno:** Monoclonal plasma cell dyscrasia has been associated with PH in patients with a POEMS syndrome. The acronym POEMS was conied by Bardwick et al. in 1980. The incidence of PH in POEMS syndrome ranges between 5 and 10%. Severe transient PH has been reported in a patient with monoclonal gammopathy and dermatomyositis. Dramatic clinical improvement and decrease of pulmonary pressure was found after treatment with cyclophosphamide and prostacyclin.

Although thalidomide-induced PH has been described during treatment for refractory MM, however an improvement in clinical conditions and pulmonary haemodynamics has been described in patients with POEMS treated with the same drug.

Review of the literature suggests that this is the first described case of a young patient with severe myeloma in whom clinical signs of right congestive heart failure secondary to severe PH were the first clinical manifestations of the disease. Careful clinical examination ruled out the diagnosis of idiopathic or thromboembolic PH and the hypothesis of POEMS syndrome was not confirmed. The dramatic response to the treatment with steroids and chemotherapeutic agents, associated with a sudden decrease of pulmonary artery pressure (about 40 mmHg in systolic pulmonary artery pressure in 10 days), suggests that vasoactive mediators released by neoplastic cells, other
than increased plasma viscosity, may have played a role in the pathogenesis of severe pulmonary hypertension. Abnormal release of proinflammatory cytokines (interleukin [IL]-1β, IL-6, and tumour necrosis factor [TNF]-α) has been reported in association with the syndrome. Feinberg et al. described a case of POEMS syndrome in which PH improved with steroids and plasmapheresis. In this patient, soluble TNF-α receptor type I (sTNF-RI), IL-6, interferon-γ, IL-2, and soluble IL-2 receptor were abnormally high at baseline normalised with steroids and plasmapheresis. The authors hypothesised that abnormal high levels of IL-6 and abnormal low levels of its soluble receptor, deficiencies corrected by treatment, may contribute to the pathogenic manifestations of POEMS syndrome with PH. We could not perform cytokine dosage in our patient, thus their role in the pathogenesis of severe pulmonary vasoconstriction remains speculative. Preliminary data suggest that vascular endothelial growth factor may play a role in the pathogenesis of POEMS. In patients without POEMS precipillary PH may rarely be related to vascular deposition of amyloid in the lungs. Shiu and McNally described severe PH in a patient with myeloma who had diffuse lung lesion. Open lung biopsy revealed severe diffuse vascular deposition of amyloid.

References