Acute respiratory failure with bilateral chylous thorax

Cinzia Longo[1]
Roberto Trevisan[1]
Rossella Cifaldi[1]
Mitja Jevnikar[1]
Rossana Bussani[2]

[1] SC of Pneumology, "Azienda Ospedaliera-Universitaria" of Trieste, Trieste, Italy
[2] SC of Pathology Anatomy, "Azienda Ospedaliera" of Trieste, Italy

Case history

A 56-year-old man was admitted to Pneumology with a severe respiratory failure with bilateral pleural effusions and parenchymal opacities (Figure 1). The clinical documentation of the patient revealed a chylous ascites about 4 years old. At the time, the patient made several gastro-enterologic check-ups: an abdomen TC, which revealed peritoneal and mesenteric thickenings; an hepatic biopsy, which revealed a "*portal lympho-histiocitic hepatitis with ductal proliferation*" in a metabolic contest of moderate hepatocellular distress, and an epiploon biopsy, which revealed "*note of aspecific inflammation, septum fibrosis and atipic mesothelial hyperplasia*". No definitive diagnosis was made.

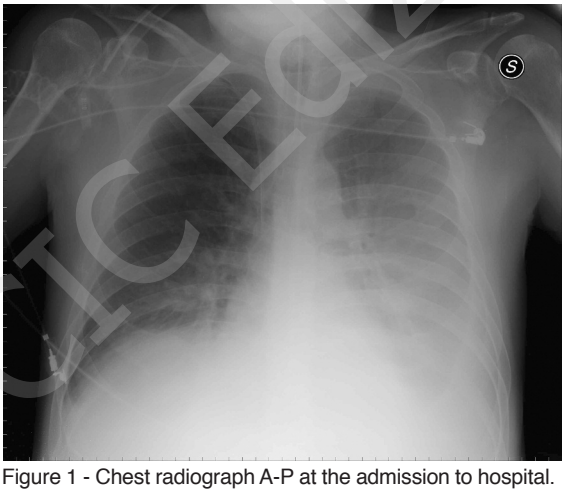

Figure 1 - Chest radiograph A-P at the admission to hospital.

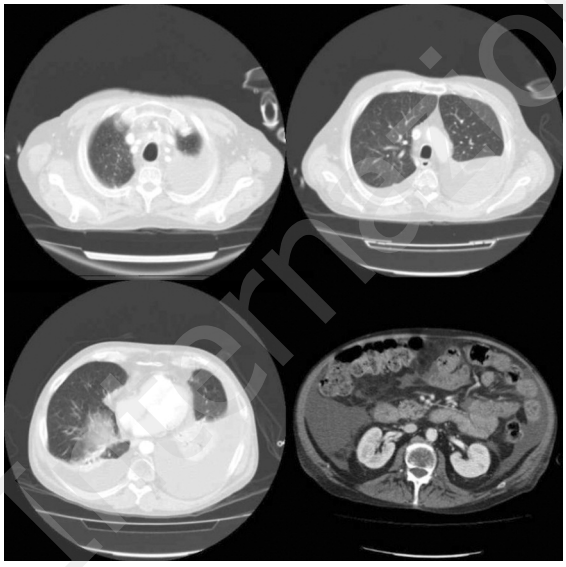

Figure 2 - Thorax and abdomen TC scan showing bilateral pleural effusion, parenchymal opacities and peritoneal effusion.

One year later the patient was admitted to the Massachussets General Hospital of Boston for a gastro-enterologic revaluation. During hospitalization, endoscopic tests revealed jejunum and ileum lymphangectasis. Ascites effusion was treated with pharmacologic therapy and periodical paracentesis. No pathology was found at thoracic level.
After clinical stabilization, the patient made a thorax TC which revealed a bilateral chylous thorax and parenchymal opacities, without focal lesions or relevant mediastinic alterations. At abdominal level there was a remarkable chylous ascites (Figure 2). Pleural and abdominal effusions were treated with thoracentesis and paracentesis respectively.
Blood tests revealed only a moderate alteration of hepatic functional indices; no alterations of tumoral markers and auto-antibody pattern were found. No relevant alterations at the bronchoscopy with BAL, nor positiveness for BK or aspecific germs at culture test were found. The cytological tests revealed a normal cellularity (for number, formula and morphology) with aspecific note of acute phlogosis. The echocardiographic report was normal.

BEFORE TURNING THE PAGE, INTERPRET THE PATIENT HISTORY, CHEST RADIOGRAPHS, THORAX AND ABDOMEN CT SCANS.

Interpretation

The patient had a history of respiratory failure, chylous thorax, chylous ascites, parenchymal opacities, a moderate alteration of liver enzymes, aspecific note of acute phlogosis at BAL.
Before the thorax CT, two clinical hypothesis were put forward: abdominal Tb or filariasis (patient has lived for a period in endemic zone), but neither was ever confirmed. Infact, nor positiveness for BK or filariasis were found.
A clinical hypothesis of systemic lymphangiomatosis was put forward on the basis of thorax CT, chylous thorax at thoracentesis and because of the clinical history of the patient (1). Being skeleton frequently involve (5), a series of bony radiography were made, but clinical suspect wasn't confirmed. For a definitive diagnosis a pleural biopsy in video-thorachoscopy was planned, but before the operation there was an inexorable decline of the patient's general conditions and, eventually, the patient died.

Diagnosis: acute respiratory failure in presence of an advanced systemic lymphangiomatosis, confirmed at autopsy

Autopsy revealed that most of the peritoneal and omento-mesenteric districts presented zones with increased consistence and reddish nodularity which measured by few millimetres to about one centimetre (Figure 3A, arrows), also with big reddish lymphatic formations (Figure 3B, arrow) and dyschromical intramural areas. There was a moderate chylousperitoneum (about 2 liter). Lungs were congested, edematous, of increased consistence, with bilateral pleural adhesions, pleural fibrinous reaction at the base of the lungs (Figures 3C and 3D) and a relevant bilateral pleural effusion. Right arterial pulmonary circle was heavily embolized. Histologically, omental and mesenteric districts and intestine presented a diffused dilatation of lymphatic vessels (Figures 4A and 4B); mesenteric lymphonodes resulted hyperplastic and characterized by large lymphangectasis. Lungs presented a massive bronchopneumonic process and lymphatic channels with thin walls, very dilated (Figures 5A e 5B) and increased for size and numerousness. The border of most of lymphatic channels proliferated in abdomen and lungs revealed multifocus positiveness at immunoenzimatic tests (technique of Biotina-ExtrAvidina (Sigma) with antibody anti CD31 (endothelial markers) [1:10, Ventana] and D2-40 [1:100, Dako]) with anti- D2-40 and CD31 (Figures 6A, 6B, 7A, 7B); in particular endothelial cells surrounding the irregular anastomosis lymphatic channels in the lungs were heavily pos-

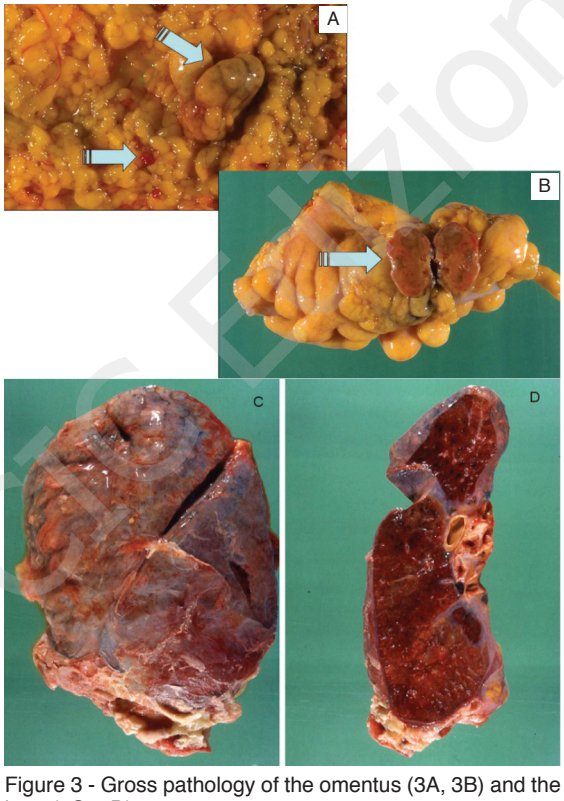

Figure 3 - Gross pathology of the omentus (3A, 3B) and the lung (3C, 3D).

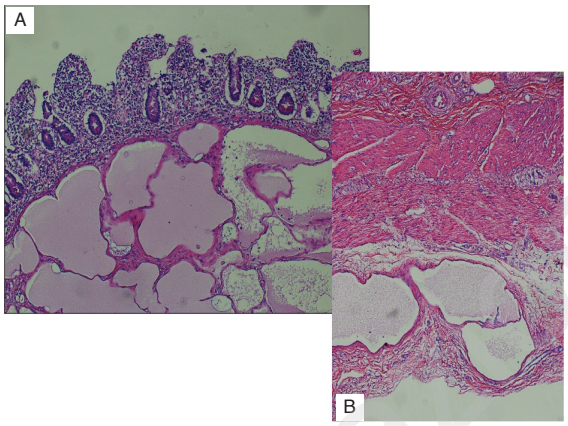

Figure 4 - Large lymphangectasias in the mucosal and sierosal district of the bowel - EE, 10x.

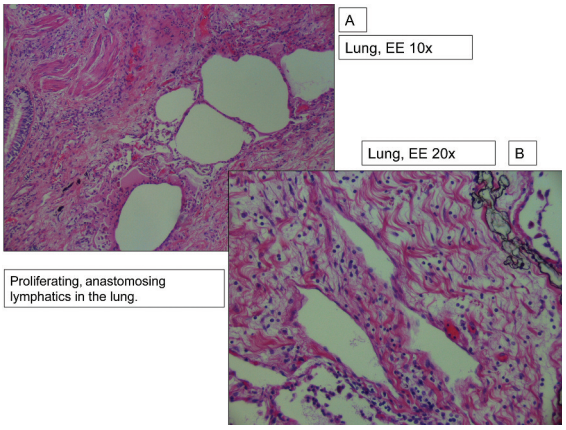

Figure 5 - Proliferating anaztomizing lymphatics in the lungs (5A emathoxylin/eosyn staining 10x, 5B emathoxylin/eosyn staining 20x).

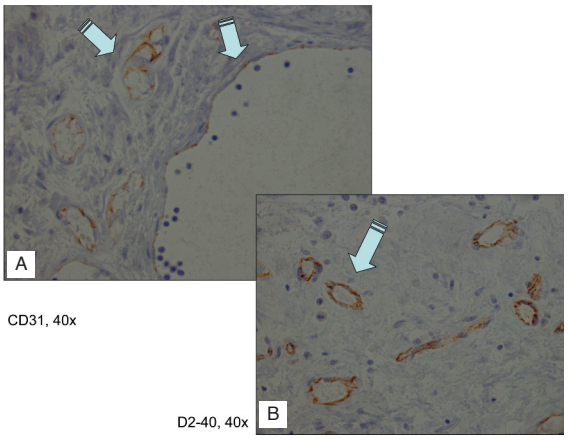

Figure 6 - Immunohystochemistry staining 40x, CD31+cells 6A, D2-40+cells 6B.

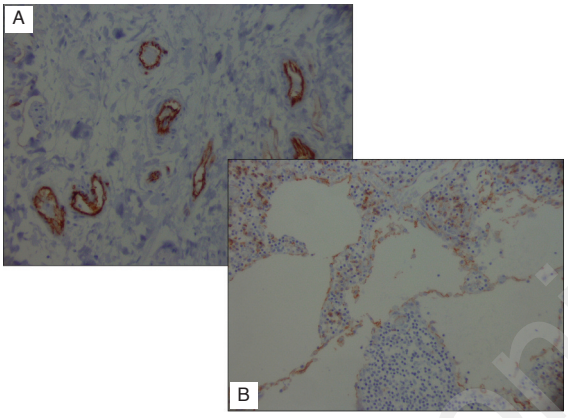

Figure 7 - Immunohystochemistry staining 40x, CD31+ cells 7A, CD2-40+ cells 7B.

itive for anti-CD31 (Figure 6A) e D2-40 (Figure 6B).
Figure 7A reveals a big positive immunoreaction with anti-CD31 also for endothelial cells of lymphatic of omentum (Figure enlarged to 20 X); instead of the Figure 7B reveals a diffused immunoreaction with anti-D2-40 of the lymphangiectasis of the mesenteric lymphonodes.

Discussion

The present case showed respiratory complications in a 56-year-old-patient with systemic lymphangiomatosis. Systemic lymphangiomatosis is a rare, misdiagnosed, disorder characterized by a diffused proliferation of lymphatic channels which frequently affects people under 20 (7.9), although some isolated cases have been reported in people as old as 80 (5-8). Disseminate form is the most common because bones are interested since the 75% of cases (5).
Disorders of lymphatic vessels must be associated with a lot of pathological conditions, such as trauma or neoplasia, or must be primitively correlated to congenital anomalous formations or idiopathic degenerations of lymphatic vessels (2-4), such as systemic lymphangiomatosis (which is different from the pulmonary lymphangiomiomatosis or LAM). Vessels proliferation could indicate a tumoral origin and the presence of destructuration found in some forms testifies to an amartomatosa origin (9). Anatomopathologically, lymphangiomatosis can be assimilable to lymphangioma (11-13); in some cases venous malformations are also given (for example vena cava left-placed) (14). At pulmonary level pathological aspects include a proliferation of lympathic anastomotic complexes with relevant expansion of lympathic ways into the lungs and mediastinum (6). Surrounding parenchyma is not spared (d.d. with *lymphangioleiomyomatosis*) but can include agglomerates of macrophages with emosiderina inside (15, 16).
Clinically, lymphangiomatosis can involve several organs containing lymphatic channels, with a particular predilection for the lungs (10, 17). A lot of patients with systemic lymphangiomatosis have asymptomatic cystic masses full of fluid and not adherent to underlying tissues. Other clinical presentations can be dyspnea, easy tiredness, chylous pericardium, chylous thorax, electrolytic and proteinous deficit, loss of weight, intermittent chest pain and dysphagia. Moreover, chyloptysis (19), hemoptysis (20), chylous ascites (4, 21), protein losing enteropathy (22), peripheral lymphedema (23), lymphopenia (24) and disseminated intravascular coagulation (25) are also described. Many patients can also experiment the onset of "wheezing" and so they can be erroneously labelled as asthmatic people before the correct diagnosis of lymphopaty is made (6).
An essential point for the diagnosis of disseminated forms is the coexistence of bone lithic lesions and chylous thorax. Diagnosis can be made with bond biopsy which reveal how these lithic lesions are lymphangioma with lymphatic fluid inside (6, 26). Lymphangiografia reveals multiple lesions of the thoracic duct, dilated lymphatic channels and lymphangioma into the bone and lung (27). Bilateral interstitial infiltrations and pericardial or pleural effusion are evident at chest radiography (18). Spirometry can reveal an obstructive-restrictive setting (6); instead HRTC reveals diffused and regular thickenings of the inter-lobular septum and of the bronco-vessel walls with a larger involving of mediastinum fat and perihilum regions (28). Hystologically, the antigens correlate to factor VIII and CD31 are useful endothelial markers for the immunohistochemical definition of these channels (29).
The natural history of this disease is characterized by a progressive growth of lympathic complexes with compression of the near structures (6, 30). Therapy could be focussed on obtaining a reduction of the symptoms due to compression and a reduction of chylous effusion (30). Success of the surgical treatment is heavily limited by the difficulty of dissociating lymphatic complexes by the normal structure with a high rate of relapses (31, 32). For patients with disseminated and advanced disease therapy is palliative, like percutaneous sclerotherapy by doxyciclin which have done good outcomes (30). Diet at elevate proteic content and medium chain triglycerides can be useful (21). Recently good results for the control of chylous effusion and disease progression (33) have been reported in a case employing talidomide, a drug with immunomodulatory, antiphlogistic and antiangiogenetic actions (34). Unfortunately the case reported is only an isolated one and other investigations and con-

trolled studies will be required, which are made difficult by the fact that this pathology is quite rare, diagnosed quite late and its management is often very difficult (5). For our case report, analyzed at the end stage, after 5 years from the onset of the symptoms, no therapy was possible because of the quick and irreversible course of the events leading to the patient's death.

References

1. Miller WS. The lymphatics and lymph flow in the human lung. Am Rev Tuber 1919;3:193-209.
2. Hilliard RI, McKendry JB, Phillips MJ. Congenital abnormalities of the lymphatic system: a new clinical classification. Pediatrics 1990;86:988-994.
3. Levine C. Primary disorders of the lymphatic vessels a unified concept. J Pediatr Surg 1989; 24:233-240.
4. Smeltzer DM, Stickler GB, Fleming RE. Primary lymphatic dysplasia in children: chylothorax, chylous ascites, and generalized lymphatic dysplasia. Eur J Pediatr 1986;145:286-292.
5. Faul JL, Berry GJ, Colby TV, et al. Thoracic lymphangiomas, lymphangiectasis, lymphangiomatosis and lymphatic dysplasia syndrome. Am J Respir Crit Care Med 2000;161(3 pt 1):1037-46.
6. Tazelaar HD, Keer D, Colby TV, et al. Diffuse pulmonary lymphangiomatosis. Hum Pathol 1993;24 (12):1313-22.
7. Tran D, Fallat ME, Buchino JJ. Lymphangiomatosis: a case report. South Med J 2005;98(6):669-71.
8. El Hajj L, Mazières J, Didier A, et al. Diagnostic value of bronchoscopy, CT and transbronchial biopsies in diffuse pulmonary lymphangiomatosis: case report and review of the literature. Clin Radiol 2005;60(8):921-5.
9. Takahashi K, Takahashi H, Dambara T, et al. An adult case of lymphangiomatosis of the mediastinum, pulmonary interstitium and retroperitoneum complicated by chronic disseminated intravascular coagulation. Eur Respir J 1995;8(10):1799-802.
10. Rebollo MG, Olivera MJ, Nieto S, et al. Linfangiomatosis pulmonar difusa. Rev Patol Resp 2004; 7(1):29-31.
11. Enzinger, FM, Weiss SW. Tumors of lymph vessels. In S. M. Gay. Soft Tissue Tumors. editor Mosby, St. Louis, 1995:679-700.
12. Ramani P, Shah A. Lymphangiomatosis: histologic and immunohistochemical analysis of four cases. Am J Surg Pathol 1993;17:329-335.
13. Carlson KC, Parnassus WN, Klatt EC. Thoracic lymphangiomatosis. Arch Pathol Lab Med 1987;111:475-477.
14. Jackson IT, Carreno R, Hussain K, et al. Hemangiomas, Vascular malformations, and lymphovenous malformations: classification and methods of treatment. Plast Reconstr Surg 1993;91:1216-30.
15. Kalassian KG, Ruoss S, Raffin TA, et al. Lymphangioleiomyomatosis: new insights. Am J Respir Crit Care Med 1997;55:1183-1186.
16. Taylor JR, Ryu J, Colby TV, et al. Lymphangioleiomyomatosis: clinical course in 32 patients. N Engl J Med 1990;323:1254-1260.
17. Rosai J. Lymph vessels. In J. Rosai. Ackerman's Surgical Pathology. Mosby editor, St. Louis, 1995: 2221-2226.
18. White JE, Veale D, Corris PA, et al. Generalised lymphangiectasia: pulmonary presentation in an adult. Thorax 1996;51:767-768.
19. Sanders JS, Rosenow EC, Brown LR, et al. Chyloptysis (chylous sputum) due to thoracic lymphangiectasis with successful surgical. Arch Intern Med 1988;148:1465-1466.
20. Bresser P, Kromhout JG, Verhage TL, et al. Chylous pleural effusion associated with primary lymphedema and lymphangioma-like malformations. Chest 1993; 103:1916-1918.
21. Calabrese PR, Frank H, Taubin HL. Lymphangiomyomatosis with chylous ascites: treatment with dietary fat restriction and medium chain triglycerides. Cancer 1977;40:895-897.
22. Scully RE, Mark EJ, McNelly BU. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 8-1984: an elderly woman with proteinlosing enteropathy and pleural effusions. N Engl J Med 1984;310: 512-520.
23. Duhra PM, Quigley EM, Marsh MN. Chylous ascites, intestinal lymphangiectasia and the "yellow-nail" syndrome. Gut 1985;26:1266-1269.
24. Vardy PA, Lebenthal E, Shwachman H. Intestinal lymphangiectasia: a reappraisal. Pediatrics 1975;55: 842-851.
25. Dietz WH Jr, Stuart MJ. Splenic consumptive coagulopathy in a patient with disseminated lymphangiomatosis. J Pediatr 1977;90:421-423.
26. Vogt-Moykopf I, Rau B, Branscheid D. Surgery for congenital malformations of the lung. Ann Radiol (Paris) 1993;36:145-160.
27. Jang HJ, Lee KS, Han J. Intravascular lymphomatosis of the lung: radiologic findings. J Comput Assist Tomogr 1998;22:427-429.
28. Valentine VG, Raffin TA. The management of chylothorax. Chest 1992;102:586-591.
29. Hillerdal G. Chylothorax and pseudochylothorax. Eur Respir J 1997;10:1157-1162.
30. Molitch HI, Witte C, vanSonnenberg E, et al. Percutaneous sclerotherapy of lymphangiomas. Radiology 1995;194:343-347.
31. Dunkelman H, Sharief N, Berman L, et al. Generalised lymphangiomatosis with chylothorax. Arch Dis Child 1989;64:1058-1060.
32. Gilsanz V, Yer HC, Baron MG. Multiple lymphangiomas of the neck, axillae, mediastinum and bones in an adult. Radiology 1976;120:161-162.
33. Rachel Pauzner, Haim Mayan, Ana Waizman, et al. Successful Thalidomide Treatment of Persistent Chylous Pleural Effusion. Annals of Internal Medicine 2007;146(1):75-76.
34. Matthews SJ, McCoy C. Thalidomide: a review of approved and investigational uses. Clin Ther 2003; 25:342-95.