Atypical presentation of pulmonary hemosiderosis accompanied by tuberculosis pneumonia in childhood: Cause or association?

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Abstract
Pulmonary hemosiderosis (PH) is a rare and often fatal disease characterized by repeated episodes of intra-alveolar bleeding that leads to abnormal accumulation of iron as hemosiderin in alveolar macrophages and subsequent development of pulmonary fibrosis and severe anemia.
Commonly it can occur as a primary disease of the lungs, especially in children, or as a secondary complication of cardiovascular or systemic diseases. Typically a triad of hemoptysis (not always present in children), iron deficiency anemia, and diffuse pulmonary infiltrates characterizes pulmonary hemosiderosis. It is the absence of diagnostic features combined with the clinical picture that constitute the diagnostic criteria for these disorders. Because of difficulties in pinpointing a specific cause of pulmonary hemosiderosis, it remains a very difficult disease to identify, continuing to be a diagnosis of exclusion.
We report a case of atypical clinical presentation of pulmonary hemosiderosis accompanied by tuberculosis pneumonia diagnosed in a twelve year-old child based on hemosiderin-laden macrophages (HLM) and a positive polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* in bronchoalveolar lavage (BAL), simultaneously.

Key words
Pulmonary hemosiderosis, hemosiderin-laden macrophages, *Mycobacterium tuberculosis*, tuberculosis pneumonia, polymerase chain reaction, bronchoalveolar lavage

Resumen
La hemosiderosis pulmonar es una enfermedad rara y con frecuencia mortal, caracterizada por episodios repetidos de sangrado intra-alveolar que conduce a una acumulación anormal de hierro como hemosiderina en los macrófagos alveolares y el consiguiente desarrollo de fibrosis pulmonar y anemia.
Generalmente ocurre como una enfermedad primaria de los pulmones, especialmente en niños o como una complicación secundaria de enfermedades cardiovasculares o sistémicas. La hemosiderosis pulmonar se caracteriza por la tríada de hemoptisis (no siempre presente en niños), anemia por deficiencia de hierro e infiltrados pulmonares difusos. La ausencia de características diagnósticas, combinada con el cuadro clínico constituyen los criterios diagnósticos de esta enfermedad. Debido a la dificultad para determinar una causa específica de la hemosiderosis, ésta sigue siendo una enfermedad muy difícil de identificar y se continúa haciendo el diagnóstico por exclusión.
Reportamos un caso de presentación clínica atípica de hemosiderosis pulmonar, acompañada de neumonía por tuberculosis, diagnosticada en un niño de 12 años de edad sobre la base del hallazgo de macrófagos cargados de hemosiderina y un resultado positivo de *Mycobacterium tuberculosis* en la reacción en cadena de la polimerasa en un lavado broncoalveolar, simultáneamente.

Palabras clave
Hemosiderosis pulmonar, macrófagos cargados de hemosiderina, *Mycobacterium tuberculosis*, neumonía por tuberculosis, reacción en cadena de la polimerasa, lavado broncoalveolar.

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■ INTRODUCTION

Pulmonary hemosiderosis (PH) is a rare and often fatal disease characterized by repeated episodes of intra-alveolar bleeding that lead to abnormal accumulation of iron as hemosiderin in alveolar macrophages and subsequent development of pulmonary fibrosis and severe anemia (1).

The first pathologic description of this disease was by Dr. Virchow in 1864. In 1918, Dr. Goodpasture indicated an association of pulmonary hemorrhage with glomerulonephritis, thus leading to the naming of this form of the disease after him. Dr. Celeen, in 1931, described the clinical presentation of the disease, and, finally, in 1962, Dr. Heiner proved that elimination of cow's milk from the diet could improve the symptoms of many patients (2).

It commonly manifests itself as the typical triad of hemoptysis (not always present in children), anemia and diffuse parenchymal infiltrates on chest radiography. Hemosiderin is formed by the breakdown of red blood cells and iron release from the heme group. It reflects an alveolar abnormality, which may be a primary condition or secondary to systemic disease. In general, primary pulmonary hemosiderosis is more common than the secondary types (1,3). In the secondary setting, the main causes are congenital or acquired cardiopulmonary abnormalities, infections and their complications such as bacterial pneumonias, immunologically mediated diseases, neoplasm, toxins, drugs, environmental molds and miscellaneous causes (1).

In the primary setting, genetic, autoimmune, allergic, environmental, and metabolic mechanisms of pathogenesis have been suggested, but the etiology of the primary, most common in childhood, idiopathic pulmonary hemosiderosis (IPH), remains unknown. Clinical manifestations include cough, hemoptysis, dyspnea, fever, pallor and fatigue (4).

The pathophysiology of pulmonary hemorrhage varies by etiology. Bleeding can come from inherited or acquired weakness, inflammation or congestion of pulmonary blood vessels; immune reactions or antigen-antibody complex deposition in the lung; invasive or chronic infections, or toxic reactions. This inflammatory cascade of events can trigger or activate all types of lung disease, pulmonary consolidations, and lymphadenopathy (5).

Pulmonary hemosiderosis is an uncommon finding, but the true incidence is unknown. After age 10, the male to female ratio is 2:1 (6).

Death can occur acutely from massive hemorrhage or after progressive pulmonary insufficiency and right heart failure. The available therapeutic modalities are not associated with a better outcome. The prognosis for pulmonary hemosiderosis syndromes as a group is difficult to determine because of the infrequency of the diagnosis and the variability among cases and etiologies. Considering individualities like IPH, the prognosis has always been regarded as poor, with a mean survival of 2.5–3 years after diagnosis. While in other studies it varied significantly with a five year survival rate of up to 86% and better outcome in those treated with long-term immunosuppressant therapy (7).

In view of its being a rare and fatal disease and the difficulty in determining a specific cause or association, we present the case report of a twelve year-old child with atypical pulmonary hemosiderosis accompanied by tuberculosis pneumonia diagnosed on the basis of: 1) unusual clinical feature presentation; 2) cytological findings of hemosiderin-laden macrophages (HLM); 3) and a positive polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* by bronchoscopy in a bronchoalveolar lavage (BAL), simultaneously, and 4) due to an adequate response to treatment.

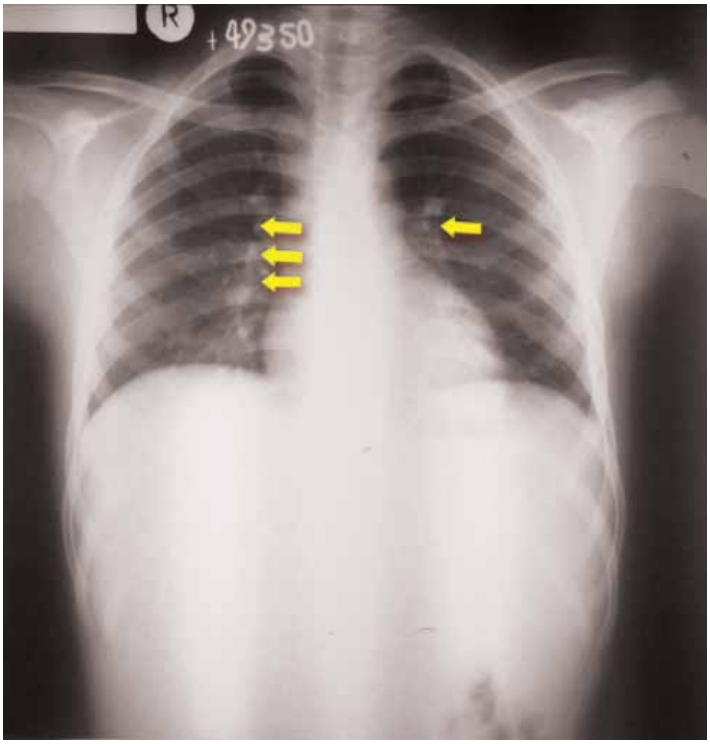
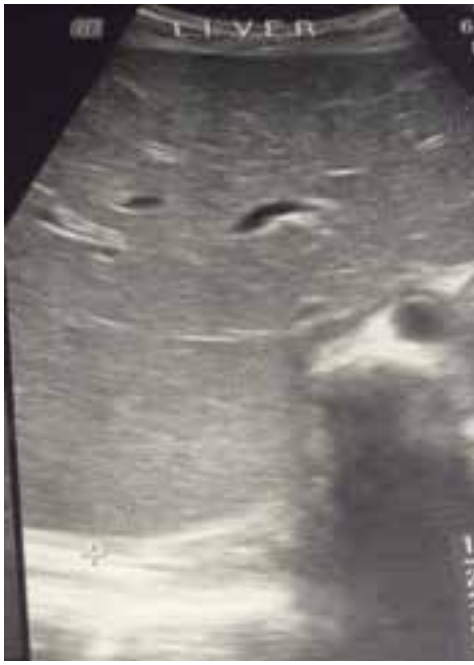


Figure1. Posterior-anterior chest X-Ray on admission, showing bilateral granuloma and hilar node calcifications (arrows). No alveolar consolidations.(Courtesy of the Corozal Community Hospital., X-ray Department)

Case Report

A 12 year-old boy, otherwise healthy and with unremarkable clinical history; referred one month prior to admission with cellulitis of the left ankle that resolved with empirical treatment with ambulatory betalactamics (penicillin for 5 days). Three weeks prior he started with onset of diarrhea, generalized malaise, light-headedness, dizziness, intermittent vomiting and low grade fevers, secondary weight loss, denying active respiratory symptoms, and with marked pallor (+++), reasons for admission.



At the time of admission in the Belize Corozal Community Hospital, the patient was neurologically conscious and alert with a Glasgow score of 15. His vital signs were temperature of 37 oC, heart rate 100 x min, respiratory rate 20 x min, and blood

Table 1. Laboratory data workup on admision

WBC	5400µ	Uric acid	5.57mg/dl
Neutrophils	13.2%	T. Prot	7.6g/dl
Lymphocytes	68.4%	Albumin	4.4g/dl
Monocytes	0%	T. Bilir	0.44mg/dl
Eosinophils	0%	AST	36.0
Basophils	0%	Direct Bilir	0.44mg/dl
Hb	4.5	ALT	13IU/
Ht	14.4%	Alk Phosp	424IU/L
MCV	105.1Fl (75-95)	Cholesterol	112.0mg/dl
MCH	32.8 (27-32)	Trig	121.0mg/dl
MCHC	31.3 (30-36)	Hepatitis A	Negative
Plt	53,000µ	Ca	8.1mg%
Blood film	*Reticulocyte count 2%* (0.5-1.5%), Blast cells negative. *Thrombocytopenia*, sickle cell negative. *Spherocytes 3+* (0-2). *Stomatocytes 3+* (0-2) *Schistocytes 1+* (0-2)	CRP	Positive
		HBsAG1	Negative
Glucose	120mg/dl	PT	14 (14) secs
BUN	6.0mg/dl	PTT	34 (34) secs
Parasitology	No ova or parasities found, negative occult blood	Coombs DAT	Negative
		Urianaysis	Normal

WBC: White blood cells, **Hb:** Hemoglobin, **Ht:** Hematocrit, **Plt:** Platelets, **BUN:** Blood urea nitrogen, **T. Prot:** Total proteins, **T. Bilir:** Total bilirrubins, **AST:** Aspartate aminotransaminase, **ALT:** Alanine aminotransaminase, **Alk Phosp:** Alkaline phosphatase, **Trig:** Triglycerides, **Ca:** Calcium, **PT:** Prothrombin time, **PTT:** Partial tromboplastin time, **CRP:** C reactive protein, **HBsAG1:** Hepatitis B surface antigen HBsAG1

pressure 100/67 mmHg. Clinically the patient had well hydrated mucosae, pallor (+++), well ventilated lungs with no signs of alveolar occupation (chest X-ray in Figure 1), rhythmic heart beat, mild generalized abdominal tenderness without rebound, pronounced hepatomegaly, 6 cm and 4 cm, respectively, with ultrasound confirmation (Figure 2), normal genitalia, no peripheral edema or active hemorrhagic events with a capillary refill of 3 x min. Based on the clinical presentation, a complete laboratory workup was done which depicted severe hemolytic anemia with reticulocytosis, spherocytocis, stomatocytocis, thrombocytopenia and negative blast and sickle cells in a peripheral blood smear. Urinalysis and liver and kidney function tests, were within the normal limits, ruling out active bleedings. The serology for hepatitis B and C and the stool test for occult blood were negative (Table 1). Due to high risk of further hemolysis, no blood transfusion was indicated and methylprednisolone pulses were initiated. During his four-day stay, the patient was hemodynamically stable with normal vital signs at all times, reason why he was discharged. Oral prednisone and folic acid were continued ambulatory with temporary response to treatment. At the five-day follow up visit to the clinic, the patient referred mild generalized weakness, occasional low grade fever, and further hemolysis with hematocrit of 13% accompanied by leukopenia (1,600) and partial recovery of platelet count (114,000). This prompted further evaluation and diagnostic confirmation by the Department of Oncology-Hematology in Chetumal and then in Mérida, Mexico.

Prior to his admission at the General Hospital of Chetumal, corticosteroids were suspended for one week in order to carry out a bone marrow aspirate. During that time span, the patient started to deteriorate presenting intermittent fevers, generalized weakness, and respiratory distress on exertion, productive cough and signs of anemic crisis requiring multiple blood transfusions. Lymphoproliferative disorders such

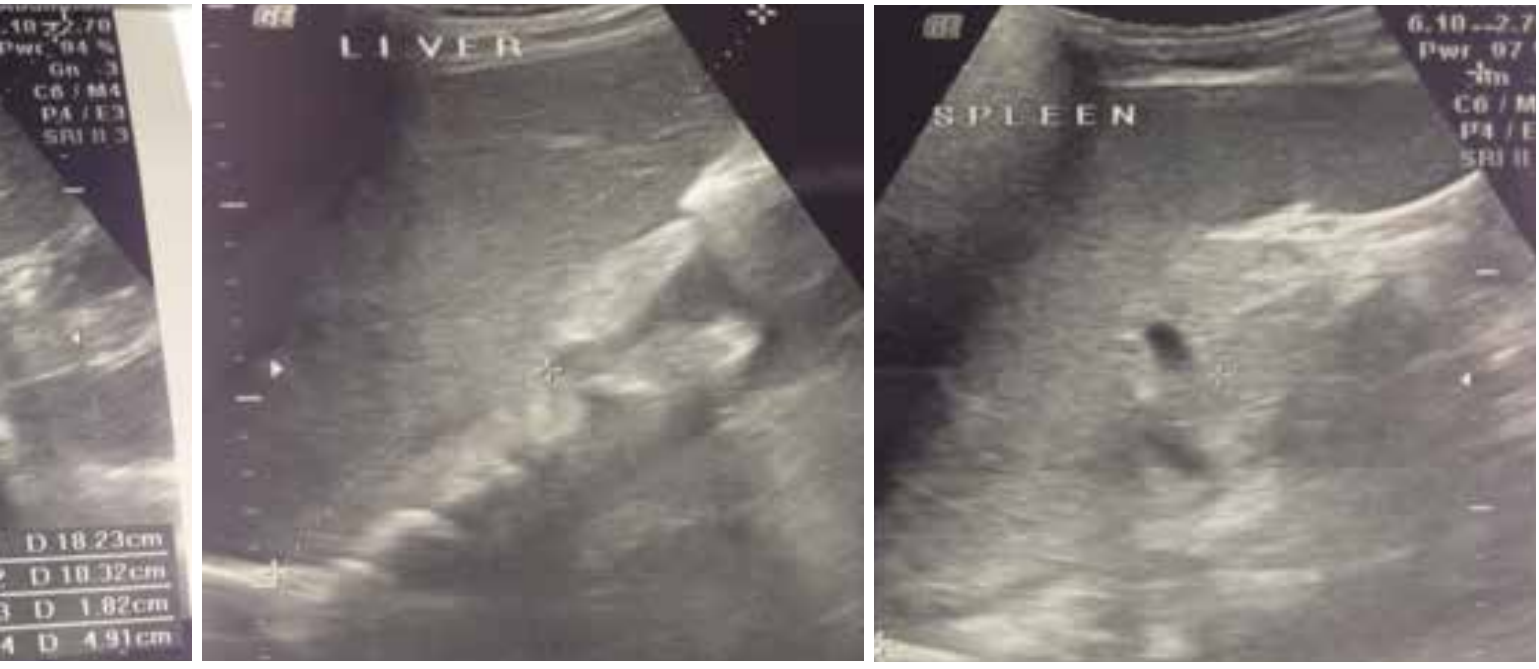


Figure 2. Ultrasound images show liver and spleen enlargement.

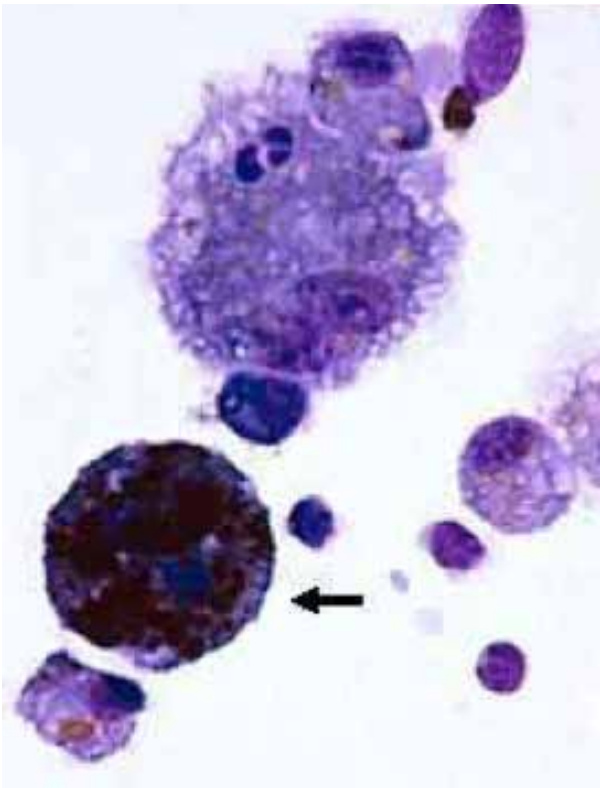


Figure 3. Microphotograph illustrates a macrophage that contains hemosiderin pigment (arrow) using Wright's stain (Courtesy: http://www.medvet.umontreal.ca/clinpath/banq-im/Images/cyto12fleche.jpg)

as leukemia were ruled out by negative bone marrow aspirate. Another ultrasound of liver and spleen was performed at that hospital finding hepatic lesion of the right lobe by CT-scan suggestive of a solid tumor mass, probably hepatocarcinoma, as well as nodular pulmonary lesions by X-ray. The patient was referred to the Oncology Department of the third level General Hospital O'Horan in Mérida for diagnostic confirmation. At this institution, oncologic and hematologic disorders were ruled out. Patient received interconsultation with the Pediatric Surgery Department suggesting liver abscess requiring only conservative treatment with metronidazole, which resolved. The patient then deteriorates and is admitted to the pediatric intensive care unit for developing multiple foci pneumonia and probable systemic mycosis infection refractory to treatment that required multiple antibiotic regimes such as vancomycin, amikacin, cefepime and amphotericin B. During this therapy course of 3 weeks, the patient continued presenting febrile peaks, active respiratory symptoms, denied hemoptysis, with negative blood cultures, acid-fast bacilli (AFB) smears, sputum culture and HIV test. Based on the patient's poor clinical condition and outcome, a bronchoscopy and bronchoalveolar lavage were indicated. The cytological findings of the sputum were hemosiderin-laden macrophages (HLM) (Figure 3), suggestive of pulmonary hemosiderosis and a positive PCR for *Mycobacterium tuberculosis*. Prednisone and anti-tubercular treatment were initiated, respectively, with observation of clinical improvement after one week of treatment. The patient was discharged with both medications and the follow-ups have been unremarkable and uneventful.

■ DISCUSSION

The term hemosiderosis is derived from the Greek words, hemo (blood) and sideros (iron), and the disease is characterized by the focal or generalized accumulation of iron in the form of hemosiderin (9). Hemosiderin is an intracellular storage form of iron (> 33% iron by weight) and contains ferric hydroxides, polysaccharides, and proteins that can reside for up to 4–8 weeks in the lungs. Pulmonary hemosiderosis is considered idiopathic (also known as Ceelen-Gellerstedt's syndrome) if no other cause is identified, and if the lung biopsy excludes capillaritis, granulomas, or other immune depositions.

Due to the fact that our patient came with sole presenting features of hepato-splenic anemia and inactive pulmonary symptoms, we were encouraged to pursue a more hematological and oncological approach as study protocol.

It is common for patients with PH to have delayed diagnosis. The diagnosis is often missed because the bleeding can be covert, and hemoptysis is often missing, as in the present case. It seems that the use of corticosteroids at first contact with this patient would have probably greatly benefitted him, preventing him from ever presenting life-threatening pulmonary bleeding, even though it was used for a different purpose as in hemolytic anemia.

According to the pathophysiology, it has been recognized that hemosiderin deposits can reside in the lungs for a long period of time, from 4–8 weeks. Infectious pneumonia, bronchitis, aspiration, asthma and cystic fibrosis with many of the same complaints and findings are more common. This acute inflammatory cascade of events can trigger or activate all types of lung disease, pulmonary consolidations, and lymphadenopathy as described by Sheets (5). In our setting the patient did not present active pulmonary symptoms by clinical and radiography evaluation on his first admission. With hindsight, after the positive PCR to *M. tuberculosis* found in BAL, we intentionally retrieved his chest X-ray file observing hilar node calcifications (Ranke complex and Ghon lesion granulomas) to our bewilderment, suggestive of primary pulmonary tuberculosis as the secondary cause or association of PH. It is well documented by Bouomrani and colleagues (10) that various other causes of recurrent alveolar hemorrhage can be attributed to infections like pulmonary tuberculosis. This association is also mentioned by Kamal Kumar Singhal (8) in his letter to the editors stating that, epidemiologically, tuberculosis in India would be a more relevant cause for secondary hemosiderosis and that being a paucibacillary disease, microbiological diagnosis in children is challenging (8).

Although the polymerase chain reaction, according to the WHO guidelines, is not routinely done to diagnose tuberculosis in the pediatric population, it has a sensitivity of 40% and a specificity of 80% for detecting *M. tuberculosis* in children, compared to 37% of culture and may strengthen and hasten clinical diagnosis in culture-negative patients (11). In our setting, pulmonary tuberculosis was diagnosed by this method through deliberate search in a BAL sputum test by bronchoscopy, after the arduous struggle with refractory pneumonia unresponsive to treatment challenges and due to

culture and AFB negative specimen results obtained before. The presence of hemosiderin-laden macrophages in BAL in children is considered to be pathognomonic for this disease with a high sensitivity of 1 and high specificity of 0.96 as described by Zeynep and colleagues (12). We highlight the importance of the accurate and timely diagnosis of pulmonary hemosiderosis that can be made, which may influence the treatment and long-term prognosis of the patient.

■ CONCLUSION

In this particular case, pulmonary hemosiderosis, a rare and fatal disease, continues to be a diagnostic challenge of exclusion in view of the difficulty it represents in pinpointing a specific cause or association and because of its atypical presentation. Pulmonary tuberculosis in children continues to be a diagnostic challenge even for the most skilled clinicians in this paucibacillary disease, because of the pitfalls that, if not taken into consideration, can be encountered during its early or delayed detection. Our patient received prompt medical attention with corticosteroids as the mainstay of treatment for pulmonary hemosiderosis and anti-tubercular therapy for tuberculosis. This was reflected in the good clinical outcome of our patient. The patient's clinical follow-ups have been unremarkable and uneventful up to date.

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