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CASE REPORT

Littoral cell angioma of the spleen accompanied by haemophagocytic syndrome in a dialysis patient suffering from AA amyloidosis

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ABSTRACT

Littoral cell angioma (LCA) is a rare form of vascular tumor unique to the spleen that arises from the specialized endothelial cells that line the splenic sinuses (littoral cells). Haemophagocytic syndrome (HS) is also a rare hematologic disorder that some times accompanies LCA. The authors describe a young dialysis patient with a history of familiar mediteranean fever and secondary amyloidosis who was found to have this rare association of AA amyloidosis with LCA and haemophagocytic syndrome.

KEY WORDS: *AA amyloidosis, Littoral cell angioma, Spleen, Haemophagocytic syndrome. Haemodialysis*

INTRODUCTION

Littoral cell angioma (LCA) is a rare form of vascular tumor unique to the spleen that arises from the specialized endothelial cells that line the splenic sinuses (littoral cells) [1-3]. Macroscopically LCAs are characterized by the presence of one or multiple well circumscribed nodules in the spleen [3-5]. Their localization is consistent with their mixed endothelial and histiocytic immunophenotype. LCAs are usually identified following splenectomy [1-5].

Haemophagocytic syndrome (HS), also referred to as haemophagocytic lymphohistiocytosis or macrophage activation syndrome, comprises a heterogeneous group of disorders [6]. It is a rare hematologic disorder characterized by reduction of at least 2 of the series of peripheral blood cells with an increase of macrophages (>3%) of bone marrow cells and/or their presence in liver and spleen accompanied by systemic symptoms i.e. fever, rash, lymphoadenopathy etc. It is mainly secondary to infections, collagen and malignant diseases or to a combination of these. This syndrome often accompanies LCA. It is rarely familial in children (autosomic recessive character due to mutation of perforine gene) where is resistant to treatment. Pathogenesis is linked to a reduction or absence of cytotoxic activity of Natural Killer (NK) and CD8+ lemphocytes, which is regressive in secondary forms but not in familial cases [6]. To our knowledge there are no cases in the medical literature of dialysis patients suffering from LCA and haemophagocytic syndrome together with secondary amyloidosis. We describe a young dialysis patient with a history of familiar mediteranean fever

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and secondary amyloidosis who was found to have LCA accompanied by haemephagocytic syndrome.

CASE REPORT

HISTORY:

A 28-year-old patient presented in May 2004 with a 2-week history of fever (up to 39°C) without any other complaints. He denied of having coughing, shortness of breath, headache, diarrhea or any other specific symptoms. The patient had been on hemodialysis for the last 2 years due to AA amyloidosis that had been attributed (based on his past medical history and histology that included recurrent attacks of serositis and fever resolving after treatment with colchicines) to Mediterranean fever. Mutation analysis in exons 2, 3, 5 and 10 of the Marenostrin Encoding Fever gene (MEFV) that covers 93% (27/29) of published mutations was negative. Despite this, the diagnosis of Meditteranean fever was done based to his clinical course and histological findings of AA amyloidosis (renal, vessels).

Four months before his recent admission, the patient had been also hospitalized in the Renal Department for an upper respiratory tract infection accompanied by hemophagocytic syndrome. Extensive workup during that hospitalization revealed only a single hypoattenuated lesion of the spleen of 2.6cm diameter. The patient was treated with oral prednisone, Granulocyte Colony Stimulating Factor and I.V. immunoglobulin and improved rapidly, so the finding of the spleen wasn't attributed to his symptoms and he was discharged. Since then he was on a low dose prednisone free of symptoms and with a normal second bone marrow aspirate.

On his recent second admission to the renal department, the patient was pale with a temperature of 38.5°C. Physical examination revealed no other abnormality apart from marked hepatosplenomegaly. His blood tests showed a fall in all blood series and a bone marrow aspirate confirmed the recurrence of hemophagocytic syndrome. On the 5th day of his hospitalization and while extensive workup was under way, the patient developed neck stiffness and disorientation. A CT scan of the brain was normal and lumbar puncture showed the following results: 1030 cells/mm^3 (80% neutrophils), Glucose = 35 mg/dl, Protein 460 mg/dl while Gram stain and culture were negative. The patient received empirically ampicillin, ceftriaxone for a possible infection and γ-globulin for his hemophagocytic syndrome. Within the next few days he clinically improved regaining orientation while his fever and hemophagocytic syndrome persisted. A new CT scan of the abdomen showed multiple hypoattenuated lesions of the spleen with peripheral enhancement. The radiological impression was of multiple splenic abscesses. The fever persisted for another 15 days, with no obvious cause, infectious or no, responsible for his severe clinical state. The introduction of broad-spectrum antibiotic treatment plus an empirical trial of colchicine did not regress the clinical syndrome. Splenectomy was decided and performed.

PATHOLOGY:

The resected spleen weighed 800 g. The splenic parenchyma was occupied by 7 well circumscribed nodules ranging in size from 0.8 to 1.7 cm. Microscopically the nodules corresponded to a complex anastomosing network of vascular spaces of varying size, some with narrow compressed lumens, others composed predominantly of large dilated blood-filled spaces, or characterized by papillary projections. A single layer of endothelial cells lined the vascular channels. Mitotic figures and nuclear pleiomorphism or atypia were not seen. Numerous exfoliated lining cells were also observed within the vascular spaces. The exfoliated cells showed a macrophage/histiocyte-like morphology showing hemophagocytosis, prominent hemosiderin deposition and foamy cytoplasm [Fig. 1a]. Immunophenotypically the lining cells showed positive staining for the vascular markers CD31 [Fig. 1b] and factor VIII related antigen as well as for the myelomonocytic marker CD68 and focally for the C3d complement receptor CD21 [Fig. 1c]. The endothelial cells as well as the exfoliated cells were negative to CD34 and CD8 antibodies. The wall of small vessels, stain positive for Congo red and for AA amyloid. The rest of the splenic parenchyma retained its normal architecture, while the red pulp was hyperplastic and the sinusoids showed hemorrhagic congestion. Based on the immunomorphological findings a diagnosis of multiple Littoral Cell Angioma (LCA) and AA amyloidosis was established.

POSTOPERATIVE COURSE:

During the first postoperative day the patient had 3 episodes of cardiac arrest that were successfully treated. The patient transferred to ITU being dependent on inotropic support

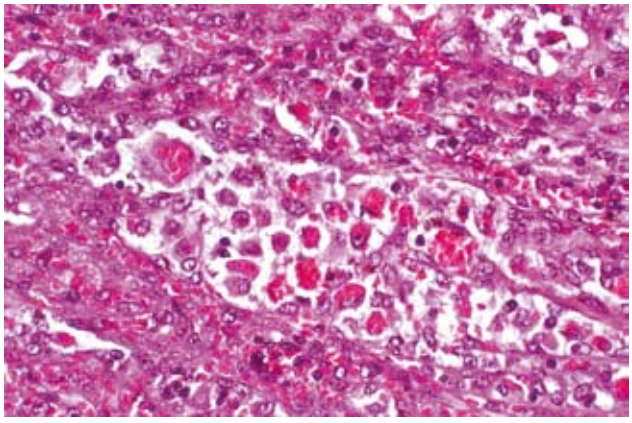

FIGURE 1A. Vascular spaces of varying size, presence of numerous exfoliated lining cells and hemophagocytosis ×40 H-E.

FIGURE 1B. Immunoreactivity of endothelial cells of angioma with CD31 antibody Envision ×5.

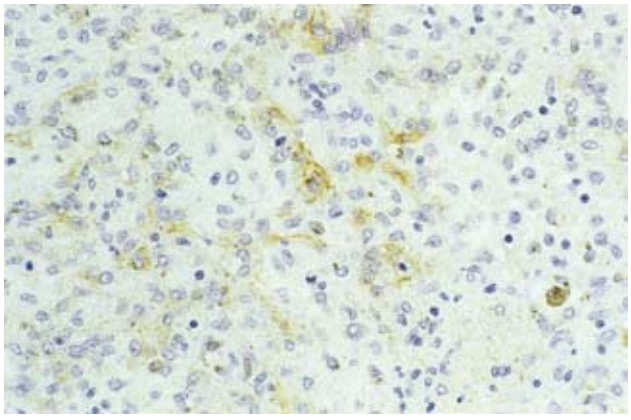

FIGURE 1C. Focal positivity of endothelial cells of angioma with CD21 antibody Envision ×20.

and mechanical ventilation. Since no metabolic causes for the cardiac arrest were identified, a thorough hemodynamic investigation was carried out (including right and left cardiac catheterization and ECHO). The findings were compatible with septic shock while echocardiography suggested the presence of cardiac amyloidosis. Despite intensive care the patient developed ARDS and died three days later.

No post mortem examination was carried out in respect to the relatives will.

DISCUSSION

Vascular tumors of the spleen are usually benign and include hemangiomas and hamartomas. In rare cases malignant angiosarcomas and/or hemangioopericytomas are discovered [7]. LCA is a rare form of vascular tumor (unique to the spleen) that arises from the specialized endothelial cells that line the splenic sinuses (littoral cells) [1-5]. Macroscopically LCAs are characterized by the presence of one or multiple well-circumscribed nodules ranging in size from 0.2 to 9 cm. Their localization is consistent with their mixed endothelial and histiocytic immunophenotype. In immunohistochemical analysis LCAs stain positive for the vascular markers CD31 [figure 1b], Factor VII related antigen and Ulex europeaus Lectin I while CD34 is only occasionally identified in basal flattened endothelial-like cells. Most lesions stain also positive for CD68, a_1-antichymotrypsin, cathepsin–D and lysozyme. Interestingly the C3d (CR2) complement receptor CD21 is expressed in LCA lining cells, a finding that is of diagnostic importance in distinguishing LCA from other splenic tumors [figure 1c] Almost all cases of splenic littoral cell tumours hitherto described were benign except one case where LCA was associated with dissemination of the disease and the authors defined this tumour as 'littoral cell haemangioendothelioma' [6] To our knowledge, LCAs have been associated with visceral malignancies in 16 out of 56 cases reported so far, with non-Hodgkin lymphoma (n=4), colorectal adenocarcinoma (n=3) and non-small cell lung cancer (3) being responsible for the majority of cases [5,8]. Some authors recommend close follow up of these patients since the aforementioned 16 cases represent almost one third of all reported cases in the literature.

LCAs are usually identified following splenectomy; it seems that it is quite difficult to diagnose a LCA preoperatively [1,5]. However, in patients investigated for pyrexia of unknown origin (PUO), vascular tumors of the spleen should always be kept in mind especially when hemophagocytic syndrome is present [1,9]. Our case illustrates that it can be a cause of PUO and should be considered in the differential diagnosis of splenic hypodense lesions There are no any references in medical literature of the presence of LCA neither in dialysis patients nor in any case of secondary amyloidosis. However, two of the cases of LCA in literature, were reported in one patient with a renal transplant (after 13 years of transplantation not associated to malignancy) [9] and in one with chronic kidney disease and history of a treated non small-cell lung cancer [10]. The greatest problem in trying to better define and analyze these tumors is the availability of only relatively small case numbers in the litterature.

Apart from the pyrexia of unknown origin, our patient presented, in both admissions, with haemophagocytic syndrome. This, taken together with the splenic lesion identified in the abdominal CT, clearly pointed the spleen as the cause of pyrexia. In the first instance the rapid recovery following supportive therapy for hemophagocytosis, the resolution of fever and the high operative risk made us reluctant to proceed with the splenectomy. Four months later, splenectomy remained the only choice in order to diagnose and eventually treat this patient although the risks were even higher taken into consideration the presence of AA amyloidosis with systemic involvement (heart, liver, kidney) and the relative immunosuppression due

to end stage renal disease.

In conclusion, it is quite difficult to diagnose a LCA preoperatively. However, in patients investigated for pyrexia of unknown origin, accompanied by the presence of splenic nodules, vascular tumors of the spleen should always be kept in mind especially when hemophagocytic syndrome is also present, even in dialysis patients. Given that in many cases of LCA there is a co-existence of vascular malignancies, an investigation for such possibility should be carried out. In our patient, after the investigation work-up no signs of malignancy were present and secondary amyloidosis was the only entity that accompanied this young patient. In this way, this case of LCA in a dialysis patient suffering from secondary amyloidosis, is of interest and has to be reported for the completeness of the picture of such rare tumors in the medical literature and possibly drive forward a better understanding of this disease.

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