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Case report and review

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Littoral cell angioma discovered after splenectomy in a patient with non-Hodgkin lymphoma and melanoma. Case report and review.

BACKGROUND: *Littoral cell angioma (LCA) is a rare vascular primary tumor of the spleen with no more than 440 cases described so far. Although often seen as benign, it is described to have malignant potential and to be associated with other immunologic disorders or malignancies.*
CASE PRESENTATION: *We present the case of LCA in a 75-year old man with a concomitant non-Hodgkin lymphoma and medical history of malign melanoma. The tumor was discovered incidentally after splenectomy for splenomegaly and refractory thrombocytopenia. The post-operative period was uneventful.*
CONCLUSION: *Our case is the first to report an association of LCA with both lymphoma and melanoma thus far. It emphasizes the need for a thorough total body examination for synchronous diseases and close follow-up to reveal associated malignancies or immunologic disorders. Further research is required to identify etiologic and pathogenetic mechanisms behind this tumor and a common basis between the three diseases.*

KEY WORDS: Littoral Cell Angioma, Neoplasm, Splenectomy, Solid Spleen Tumor

Background

Littoral cell angioma (LCA) is a rare vascular primary tumor of the spleen. It was first described by Falk et. al in 1991 and originates from the littoral or endothelial cells that line the red pulp sinuses [1]. The exact incidence of LCA is unknown, partly due to the rarity of these tumors. A wide range is reported with the incidence varying between 0.03% to as high as 14% in one autopsy series [2]. Reports show neither gender nor age predilection [3-6].

LCA is thought to be a benign neoplasia but it is associated with immunologic disorders, non-neoplastic hematologic aberrations and visceral malignancies in a quarter of the reported cases to date, especially in the presence of a splenomegaly > 10 cm [3,7-8].
Clinically, at least half of the LCAs are latent and discovered incidentally. If symptomatic, the patient may present abdominal pain - often in the epigastric region - and fever. On further examination splenomegaly (69.7%) and clinical evidence of hypersplenism including anemia, thrombocytopenia or pancytopenia may be found [2-3].
The radiological features of LCA have been well described but there is a lack of specificity in differentiating this tumor from other primary and more common vascular splenic neoplasms, metastases, disseminated infections or sarcoidosis [4]. Usually LCA manifests as multiple lesions in the spleen, but cases with a single lesion are reported as well [3-4].
A definitive diagnosis is only possible after histopathologic examination and immunohistochemical studies. Macroscopically it is characterized by multiple variably

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sized spongious & cystic nodules on the cut. Microscopically, although composed of littoral, i.e. endothelial cells there is a hybrid endothelial & histiocytic phenotype. The immunoprofile is considered to be typical for LCA [5]. There is a co-expression of both endothelial markers like CD31 and histiocytic markers such as CD68 whereas in normal spleen red sinus shore cells only endothelial cell markers are positive [8]. On the other hand LCAs are classically negative for CD8, unlike normal littoral cells.[7]
Treatment consists of splenectomy followed by a regular follow-up to monitor recurrence, metastasis and other possible associated neoplasia's.

Case Presentation

In this article we describe the case of a 75-year old man with a medical history of malign melanoma of the back (N0) with complete remission after surgical excision, a pacemaker for auricular flutter, left adrenal hypertrophy, an appendicectomy and diverticulosis. Two years earlier, the patient presented with splenomegaly, a thrombocytopenia (platelet count 58.000/mm^3) and an normocytic anemia (hemoglobin 10,6 g/dl). In the absence of manifest lymphadenopathy, two osteomedullar biopsies were performed leading to the diagnosis of small cell lymphocytic lymphoma with unknown primary focus. Given the initial lack of symptoms, a watchful waiting strategy was chosen.
Two years later, the general condition of the patient had deteriorated sharply. There was an important weight loss of almost 20kg, asthenia and dysphagia, possibly due to compression by the spleen. The blood results showed a persisting thrombocytopenia - reason for several platelet transfusions – whereas a CT-scan demonstrated an increase of the splenomegaly up to a diameter of 17,6 cm, together with multiple hypodense nodules with microcalcifications (Fig. 1).
An initial treatment by chemotherapy was indicated. During two cycles of Mabthera-Bendamustine, there was a bad tolerance for the medication. An early re-evaluation showed no amelioration regarding the thrombocytopenia, neither for the splenomegaly. Further work-up with a PET-scan 18-FDG could not reveal an additional focus (Fig. 2).
Given the refractory thrombocytopenia in the context of splenomegaly with no other focus, a splenectomy was organized. In the meantime another cycle with Mabthera, this time without Bendamustine was administrated.
The intervention started with the embolization of the splenic artery by the interventional radiologist to reduce peroperative blood loss. The actual splenectomy was uneventful and performed by a midline laparotomy instead of laparoscopy given the splenic volume. The resected specimen had a weight of 1312 gram and measured 19,5 x 16 x 10cm.
The patient recovered well, post-splenectomy vaccinations were administered following local guidelines and the patient was able to leave the hospital after a couple of days.
The histopathologic examination didn't show lymphomatous involvement of the spleen but revealed an angioma of the splenic littoral cells. Macroscopically there was a smooth thin capsule with a brownish aspect of the parenchyma and a diffuse heterogenic pattern of

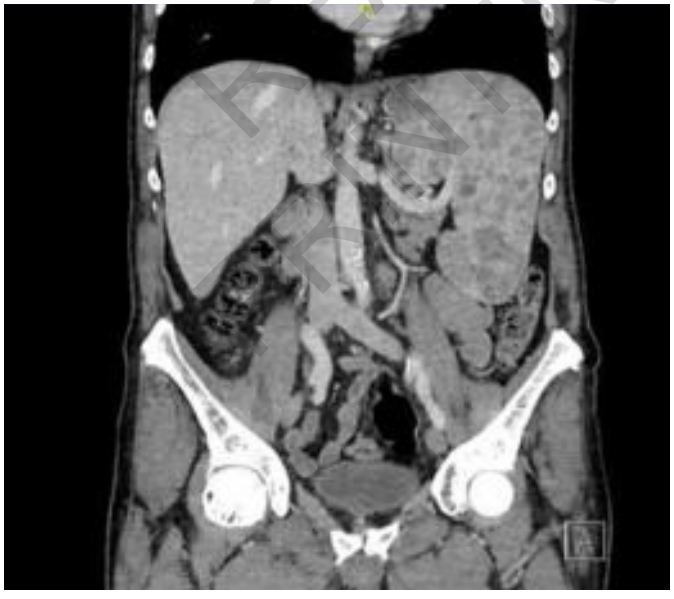

Fig. 1: The CT-scan showing the splenomegaly with a diameter of 17,6 cm.

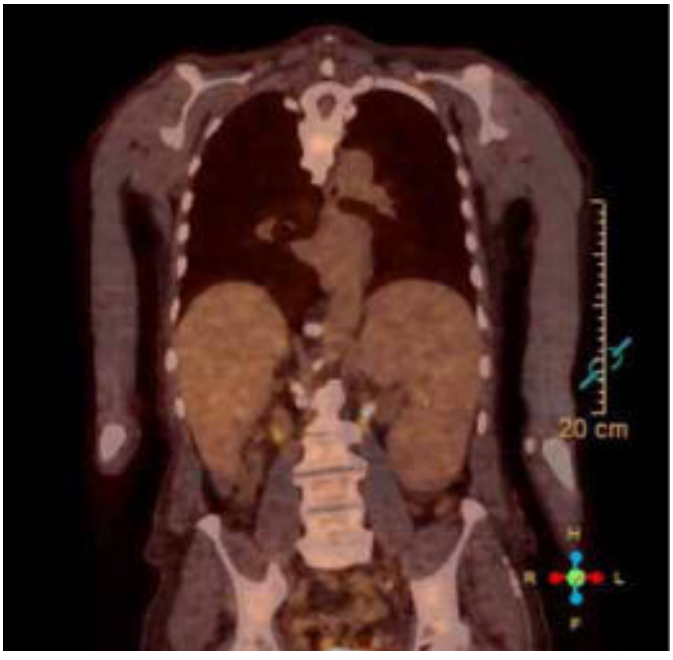

Fig. 2: The PET-scan with 18-FDG showing no a additional focus.

irregular and haemorrhagic nodules. Microscopically the nodules are formed by vascular spaces which are lined by tall endothelial cells with nuclear hypertrophy without atypia. Some cells detach the vascular lamina and show hemophagocytosis. Immunohistochemically, the specimen was positive for CD31 and CD68 and negative for CD8.

In this manner there appeared to be two synchronous diseases: the littoral cell angioma of the removed spleen and the small cell lymphocytic lymphoma demonstrated by the osteomedullar biopsy but with unknown focus.

Because postoperative blood values were normal, no further active treatment was required. A thorough follow-up was maintained however. Two years later, the patient was in relatively good general condition with a stable weight and no further complaints.

Discussion

At present, no more than 440 cases of LCA have been described so far.[3,9] Most of them are benign. However, malignant variants are reported as well, especially when the spleen weighs 1500g or is larger than 20 cm2 ($P < 0.05$) [10]. The most common location of metastasis was the liver [9]. In one case this occurred up to 4 years after splenectomy for LCA [6].

In addition, in 30% of the cases there are concomitant visceral malignancies and associated immunologic disorders. The most common of these malignancies are lymphoma, colorectal adenocarcinoma, pancreatic carcinoma, renal adenocarcinoma, gastric leiomyosarcoma, and non-small cell cancer of the lung, whereas the most frequent associated immunologic disorders are Crohn and Gaucher disease [6,9]. In literature, there are 5 cases reported of LCA associated with melanoma and 12 of LCA associated with lymphoma/leukemia. However, to our knowledge this is the only case reported where there is a triple association of LCA with both melanoma and lymphoma [3].

The etiology and pathogenetic mechanisms of LCA and it's associations are still unclear. Immune system dysregulation probably plays a role in the pathogenesis. Some evidence suggests that circulating tumor cells or immune complexes, such as in cancer or chronic infectious diseases, are filtered in the spleen, with a subsequent granulating tissue reaction that leads to a predominant vascular reactional pattern [2,9].

Since in most cases obvious specific symptoms are lacking and radiological examination shows nonspecific lesions, some other neoplasms of the spleen can give a similar appearance. The most important ones being Kaposi sarcoma, angiosarcoma and hemangiomatosis [6]. The final diagnosis depends on the histological and immunohistochemical examination. As fine-needle aspiration is not recommended due to the possibility of bleeding and malignant cell dissemination, no correct diagnosis of LCA can be established before surgery [6,11]. Because a splenectomy is also the treatment of choice, from a clinical point of view, removing the spleen is performed for both diagnostic and therapeutic purposes. It can be done laparoscopically or by open surgery depending on the situation. A laparoscopic approach by an experienced surgeon is feasible and safe in selected cases of suspected LCA, as demonstrated in a study by Cai et al [12]. However, in cases of extreme splenomegaly and extensive adhesions it can be very difficult to carry out and splenic capsule rupture with, consequently, tumor cell dissemination may lead to deterioration of oncological outcome. In these patients a hand-assisted or open approach should be favorized [6,12-13]. In our case the spleen had a diameter up to 17,6 cm, so a midline laparotomy was chosen without major complications.

The prognosis of LCA is good and there is no need for further therapy postoperatively. Because of the malignant potential of LCA and the common associated malignancies a thorough clinical evaluation and a regular follow-up is recommended, especially for those with an atypical histology.

Riassunto

BACKGROUND: L'angioma a cellule littorali (LCA) - cellule endoteliali cilindriche alte - è un raro tumore primitivo vascolare della milza con non più di 440 casi descritti finora. Anche se spesso è considerato come benigno, si ritiene possa avere un potenziale maligno e per essere associato ad altri disturbi immunologici o a tumori maligni.

Presentiamo il caso di LCA in un uomo di 75 anni con concomitante linfoma non-Hodgkin e nell'anamnesi affetto da melanoma maligno. Il tumore è stato scoperto incidentalmente dopo splenectomia per splenomegalia e trombocitopenia refrattaria. Il periodo post-operatorio è stato tranquillo.

CONCLUSIONE: il nostro caso è il primo a riportare finora un'associazione di LCA con linfoma e melanoma. Si sottolinea la necessità di un esame completo di tutto il corpo per malattie sincrone e un attento follow-up per rivelare eventuali tumori maligni associati o disturbi immunologici. Sono necessarie ulteriori ricerche per identificare i meccanismi eziologici e patogenetici alla base di questo tumore e una base comune tra le tre malattie del caso osservato.

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