Article is available online at http://www.webio.hu/por/2004/10/1/0057

CASE REPORT

Follicular Dendritic Reticulum Cell Tumor Mimicking Inflammatory Pseudotumor of the Spleen

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In the course of a routine clinical check up of the 54 year old male a splenic well circumscribed tumor like mass of 12 cm in diameter was discovered. Splenectomy with removal of splenic hilar lymph nodes and liver wedge biopsy were performed. Four years later the patient is symptom free. In the removed spleen the tumor like lesion showed a pattern consistent with the diagnosis of inflammatory pseudotumor. However, besides lymphocytes, plasma cells, macrophages, eosinophils and myofibroblasts a high number of slightly polymorphic, frequently binucleated cells positive for CD 21 and CD23 were seen. These cells which were scattered or formed smaller or larger groups and fascicles were considered to represent follicular dendritic reticulum cells (FDRCs) and the lesion a FDRC tumor. Flow cytometric DNA ploidy analysis showed a hyperdiploid cell population inside the tumor like lesion. Besides FDRC tumors of high and of intermediate malignancy the present case may represent a low grade type of moderate proliferation activity. The FDRCs of the lesion and a few smaller spindle cells were EBER positive indicative of the presence of EBV. No EBER positive cells were seen in the uninvolved spleen. (Pathology Oncology Research Vol 10, No 1, 57–60)

Keywords: Follicular dendritic reticulum cells

Introduction

Inflammatory pseudotumor (IPT) is a rare disease, occurring at virtually any site of the body and usually seen in children and younger adults. Morphologically IPT is one of the numerous spindle cell lesion with a number of variants and heterogenous concerning its histogenesis.[1,12] The predominant cell type may be the myofibroblast, the histiocyte and infrequently the follicular dendritic reticulum cell, FDRC.[3,12,14,28,35]

The borderline between histiocytic and myofibroblastic origin is not sharp, since macrophage-derived myofibroblast like spindle cells may secrete procollagen ("neofibroblasts").[21] Furthermore, FDRCs share a membrane-bound protein with fibroblasts and their processes may contain collagen type I and IV, a characteristic feature of fibroblasts, indicative of fibroblastic origin.[7,2] Recently the International Lymphoma Study Group (ILSG)[25] collected and analysed 61 tumors of histiocytic and accessory dendritic cell origin. Fife types were recognized: histiocytic tumors, Langerhans cell tumors, Langerhans cell sarcoma, interdigitating dendritic and follicular dendritic cell tumors. In this study fibroblastic reticular cell tumors, as described in 1998 by Andriko et al. were not separated.[2]

Lesions of the spleen, liver and lymph nodes. mimicking IPT may show some special features, such as predominance of FDRCs, or a FDRC tumor and the frequent presence of clonal Epstein-Barr virus genom in certain cells of the tumefactive lesion.[3,11,29]

Splenic IPT is a rare lesion, among 84 extrapulmonary IPTs only one cited. [13] Up to the year 2000 39 splenic cases have been published.[23] However, due to the application of certain immunohistochemical tests the tumors of FDRCs should be clearly separated from other types and subtypes of IPT. The electron microscopic demonstration of desmosomes in FDRCs and in their tumors is a further feature of diagnostic importance

The clinical course in most of the cases of IPT is benign. In some bacterial or viral (EBV) infection was documented.[3,10,12,16,26] However, in contradiction to the purely

Received: Oct 30, 2003; *accepted:* Jan 20, 2004

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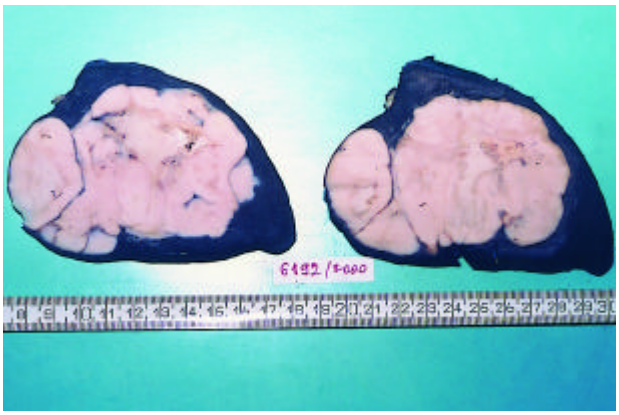

Figure 1. *Cut surface of the removed spleen„the „tumor like lesion" appears as a well circumscribed mass (12x17 cm, 580 g) and showing small necrotic foci*

inflammatory nature of IPT are individual cases with clonal cytogenetic abnormalities or aneuploid DNA values.[3,5,6,12,28,31,32] Furthermore, in a few patients metastatic dissemination or in about 25% of the cases recurrence after surgical removal were reported.[12]

The pathomechanism and prognostic significance of cases with synchronous involvement of separate lymph node groups or lymph nodes and spleen, is not clear. In a large series of FDRC tumors (17 cases) a significant recurrent and metastatic potential was seen (FDRC tumors of high and of intermediate grade).[9] Out of the 13 cases collected by the ILSG 11 were clinically evaluated, 7 were in complete remission, four patient experienced recurrences (follicular dendritic cell sarcoma). However, out of the 17 cases none were of splenic or hepatic origin and only one EBV genom positive.[25] In the present report the pathomorphological, immunohistochemical and molecular biological findings of a splenic lesion presenting as a solitary mass with EBV genom positive FDRCs are described.

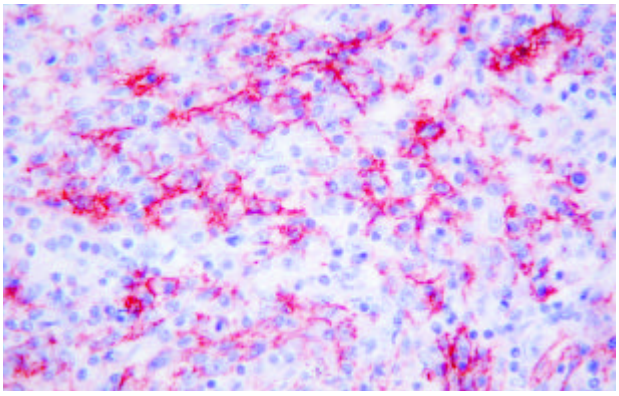

Figure 2. *Immunohistological reaction with a CD21 selective antibody. Dendritic cells showing staining of variable intensity*

Case report

The anamnesis of the 54 yr old man was negative except a short lasting febrile condition with confusion 25 yrs ago during a stay in India. At present he was seen in the course of a routine clinical check up with elevated erythrocyte sedimentation rate (68 mm/hr). Abdominal ultrasound showed enlarged hypoechoic spleen with a solitary round nodule 12 cm in diameter and hypodensity in the CT scan. Blood picture, laboratory findings were in the normal range. Splenectomy with removal of splenic hilar lymph nodes and liver wedge biopsy were performed. Four years later the patient is free of symptoms with normal erythrocyte sedimentation rate.

Materials and Methods

Immunohistochemistry was performed on formol-paraffin sections using microwave antigen retrieval with sodium citrate or EDTA. Except if otherwise indicated monoclonal antibodies of DAKO (Glostrup, Denmark) were used. After incubation with the monoclonal antibodies the sections were first treated with biotinylated antimouse-rabbit antibody and then with avidin-biotin-peroxidase complex. The bound complex was visualized by aminoethyl-carbazol- or diaminobenzidine-H2O2 reaction. EBV ribonucleic acid (EBER) *in situ* hybridisation was described elsewere.[33] Ig heavy chain (FR III) and TCR gene rearrangement was analysed according to Trainor et al,[34] DNA ploidy of the tumor like lesion and of the uninvolved spleen determined by the method of Overton et al.[24]

Histopathology

In the removed spleen – 17x11x12 cm, 580 g – a well circumscribed, but not encapsulated, lobated tumor like lesion was seen, on the cut surface greyish-white with necrotic foci (*Figure 1*). The hilar lymph nodes were 8-12 mm in size. The liver biopsy tissue did not show any macroscopical changes.

Although on inspection not encapsulated in the microscope a thin more or less continous cell-free fibrous layer separated the tumor like lesion from the neighbouring splenic tissue. At low magnification a storiform pattern, a fascicular configuration and rather loose irregular arrays of spindle cells were seen. The mass consisted of plasma cells, small nodules of lymphocytes, makrophages, few eosinophils, many myofibroblasts, small vessels and necrotic foci, surrounded by fibrous tissue with a low number of fibroblasts. Besides, rather plump slightly polymorphic cells – frequently binucleated – with an oval or round nucleus of loose or coarsely speckled chromatin pattern and conspicuous, slightly acidophilic nucleolus (HE staining) of central location were recognized. On the basis

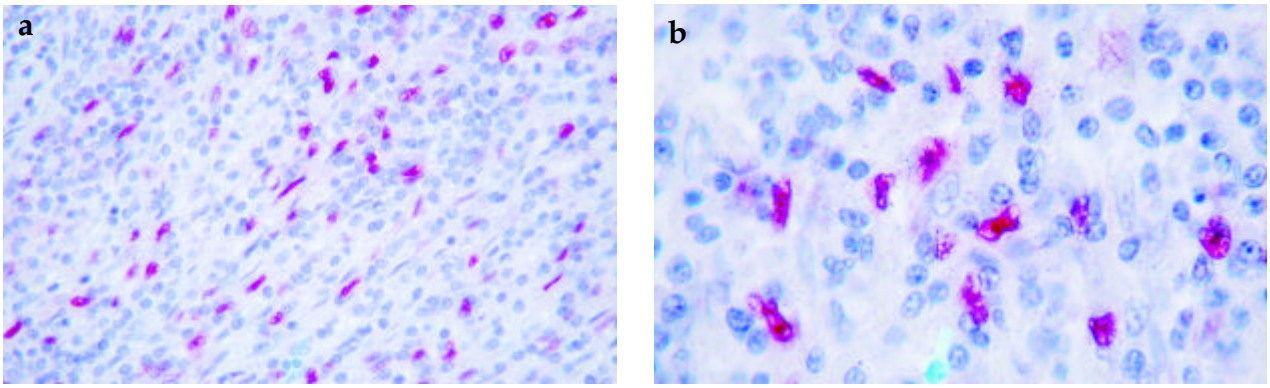

Figure 3. *EBER in situ hybridisation. A. Relatively few positive cells (x120). B. Two cell types can be distinguished, one with rather irregularly shaped nuclei (more frequent type), the other one with spindle morphology (x240).*

of their positive reaction with CD21 (*Figure 2*, C3d receptor) and CD23 (C3b receptor) selective antibodies they were considered to represent FDRCs. The distribution of these cells with many long branching cytoplasmic processes was uneven. They formed few scattered small groups and many larger bands, fascicles. Around a necrotic lesion wide layer of FDRCs was seen. A similar morphological pattern was observed in sections immunolabelled for vimentin or smooth muscle actin (SMA).

With the proliferation marker antibody MIB1 few cells were positive. Hower, the positive cells were showing features of FDRCs (slight polymorphism, 2 to 3 times larger then small lymphocytes, frequently binucleated).

The number of the lesional T cells (CD3, CD5, UCHL1) was much higher than the number of CD20 (L26) or CD79a reactive B cells. However, if the polyclonal Ig light chain reactive plasma cells were taken into account, their number equalled or even exceeded the number of T cells. These latter cells were predominantly CD8 and TIA-1 reactive. The number of TIA-1 positive granules was much higher in the lesional cells.

The rearrangement of Ig heavy chain and T cell receptor chain genes was polyclonal.

In the uninvolved splenic tissue CD21 and CD23 positive cells were only seen forming a network at the site of follicles in the Malpighian corpuscles. However, germinal centers were inconspicuous consisting of small darkly stained bcl2 positive B lymphocytes, – remnants of the mantle zones, – and showed acidophilic cell free PAS positive hyaline-fibrinoid globules and bands. The pathomechanism of the hyaline-fibrinoid change is not clear.[4]

Most of the EBER reactive cells were as a rule evenly distributed single cells. These cells, few spindle cells and many somewhat larger plump cells of irregular round or oval nuclear shape, were seen only in the tumor like lesion (*Figures 3*) and considered EBER positive FDRCs. Their number per medium power field was about 15-20 (larger cells) and 1-2 (spindle cells), respectively. No Epstein-Barr virus nuclear antigen 2 (EBNA 2) positive cells were encountered. Latent membrane protein 1 (LMP 1) was very weak or absent. Cells of the uninvolved spleen, hilar lymph nodes and liver were EBER, LMP 1 and EBNA 2 negative.

Flow cytometric analysis of DNA ploidy was performed on one and the same block containing both the well separated tumor like lesion and the uninvolved splenic tissue. If DNA (ploidy) index of the latter was considered to be 1.00, the tumor like lesion proved to be hyperdiploid, with a DNA index of 1.198

In the splenic hilar lymph nodes a heavy paracortical and medullary polyclonal plasma cell reaction was seen. In the sections of the liver no substantial changes were present.

Discussion

IPT was considered to represent most frequently a benign reactive expansile lesion of diverse confusing nomenclature.[6] However, as more and more cases were studied with adequate methods (immunohistochemistry, *in situ* hybridisation, DNA ploidy analysis, cytogenetics, non-random chromosomal aberrations, presence of clonal EBV genom) the monoclonal nature of a few cases became clear.

The histogenesis of IPT is hetereogenous, its subtypes (i.e., inflammatory myofibroblastic pseudotumor, follicular dendritic reticulum cell tumor) are usually distinguished by immunohistochemistry.

The histogenesis of the two cell types, myofibroblasts and FDRCs, is controversial.[7,21,27] The cells of myofibroblastic pseudotumors are vimentin and smooth muscle actin (SMA) positive, the FDRC lesions are in addition CD 21, CD 35, CD 23 and CNA.42 reactive.[27] Besides, FDRC lesions of the spleen and of the liver quite frequently carry the EBV genom.[3] Reactive alterations of the FDRCs were seen in angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphoma.[20,27] Atypical changes of the FDRCs or their tumors (FDRC sarcoma) are frequently associated with Castleman's disease.[8]

The present observations show that two cell types are EBER positive, many FDRCs and fewer spindle cells (*Figures 3*). Irrespective of the assumed pathogenic role of EBV, the EBER positivity of the two cell types may be indicative of their relationship. Surprisingly – as mentioned above – out of 17 FDRC tumors of intermediate or high gade malignancy none were of splenic or liver origin and only one harboured the EBV genom. Taken together these findings indicate that /1/besides intermediate and high grade tumors (sarcoma) low grade tumors of the FDRCs may also occur and /2/ FDRC tumors of the spleen, liver and lymph nodes may be EBV genom positive.

Recently it was discovered that in some cases of IPTs there is a chromosomal rearrangement involving the ALK receptor tyrosine kinase locus (band 2p23) with strong expression of ALK in the myofibroblastic spindle cells (out of 11 IPTs seven positive).[19] In the present case ALK immunohistochemistry proved to be negative.

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