Primary bilateral adrenal lymphoma revealed by hemophagocytic syndrome

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1. Introduction

Primary adrenal lymphoma (PAL) is extremely rare. So far, less than 100 cases have been described in the literature [1]. Clinical symptoms of PAL include abdominal pain, prolonged fever and weight loss [2–4]. In our knowledge, the association with hemophagocytic syndrome (HPS) was not reported. Most cases of lymphoma-associated HPS are associated with T cell or natural killer (NK)/T cell lymphoma [5]. We report a case of primary bilateral adrenal lymphoma B-cell type associated with HPS.

2. Case report

A 69-year-old woman, with a history of hypertension, diabetes and asthma, was admitted to the hospital because of fever of unknown origin for a month, anorexia, weight loss, fatigue and bi-cytopenia (normochromic microcytic aregenerative anemia: hemoglobin = 6.9 g/dl and platelet count = 39,000/mm³).

Physical examination was normal. The systematic workup of this prolonged fever was negative: hemoculture, viral serology (parvovirus B19, hepatitis B and C virus), the serology of leishmaniasis, Wright serology, tuberculin skin test and sputum Mycobacterium culture. Epstein-Barr virus (EBV) serology showed a profile of past infection (IgM anti-VCA negative, IgG anti-VCA positive and presence of EBNA antibodies).

Lumbar puncture, bone-marrow aspiration and biopsy, echocardiography and thoraco-abdominal CT scan were normal.
Evolution was spontaneously favorable with apyrexia, hemoglobin rate risen to 9.1 g/dl, after concentrated red blood cells transfusion and normal platelet count.

Four months after, the patient was readmitted because of resurgence of fever, unexplained weight loss, left flank pain and bicytopenia (Hb = 6 g/dl and platelet count = 60,000/mm³). The subsequent laboratorial study revealed hypertriglyceridemia = 6.69 mmol/L, hyperferritinemia = 3268 ng/ml, high lactate dehydrogenase (LDH) ratio = 1350 UI/L and negative Coombs test. The bone marrow aspiration revealed hemophagocytosis signs and the abdominal CT scan showed homogeneous bilateral hypertrophy of adrenal glands measuring 6.5 cm in maximum diameter. Serum cortisol concentration and urinary free cortisol, using RIA method, were normal, 145 μg/ml (normal: 75–220 μg/ml) and 50 μg/24 h (normal: 25–120 μg/24 h), respectively. A percutaneous ultrasound-guided biopsy of the left adrenal gland was performed. A diffuse large B-cell lymphoma, anti-LCA (leucocyte common antigen) and CD20-positive was diagnosed by histopathological and immunohistochemical examination (Fig. 1). EBV DNA was detected in the biopsy specimen tissue by in situ hybridation with the probe EBV encoded small nuclear early region (EBER).

A diagnosis of bilateral PAL B-cell type without concomitant localization was made because of negativity of the baseline staging (bone-marrow biopsy, thoraco-abdominal CT scan and gastroscopy).

Abdominal magnetic resonance imaging (MRI) realized 3 weeks after the diagnosis showed a bilateral adrenal hypertrophy, mesenteric adenopathy measuring about 4 cm in maximum diameter and diffuse small hepatic nodules (Fig. 2).

The patient was treated every three weeks for six cycles of CHOP (2 cycles COP then 4 cures R-mini-CEOP [Cyclophosphamide, Épirubicine, Vincristine, and Prednisone]) and
Rituximab. After one year of follow-up the patient remains free of disease with an excellent performance status.

3. Discussion

Involvement of the adrenal gland in malignant lymphoma is reported to be 25% at autopsy [4,6]. PAL is extremely rare, only 0.5% of adrenal tumors [7]. Adrenal lymphoma is often bilateral and in most of the cases of B-cell type. The primitive character of lymphoma can be retained only after having excluded another concomitant localization. In our case, the absence of other clinical and morphological involvement showed the primitive character of the adrenal lymphoma. The hepatic and ganglion involvement discovered by the nuclear magnetic resonance were considered secondary because their late appearance during the evolution.

PAL is more frequently diagnosed in men than in women; the male-to-female ratio is 2:2 and the mean age at diagnosis is 68 years. Although half of the cases described was in Japan, no ethnic predisposition is found at the moment [1,8].

The etiopathogenesis of PAL remains unknown. The temporary presence of an inflammatory focus which would be the site of a process of degeneration is the most likely hypothesis. Immune dysfunction may be a predisposing factor for PAL in some patients but no relation was able to be established [1,4]. EBV is a recognized causative agent of B-cell lymphomas, detection of EBV genome sequences and gene expression in some cases of PAL suggested its possible causative role [7,9–11]. In our case report, immuno-histochemical examination and in situ hybridization confirmed PAL B-cell associated with EBV.

Clinical presentations of PAL include:

- nonspecific clinical signs: fever of unknown origin (46% of cases), abdominal pain (26% of cases) and weight loss (24% of cases) [2,4];
- symptomatic primary adrenal insufficiency [2,3]. Latent adrenal insufficiency is noted in 2/3 of cases [12];
- fortuitous discovery by imaging techniques (incidentaloma) [7]; or rarely a palpable abdominal mass [1].

The biopsy of adrenal gland, realized after exclusion of pheochromocytoma and other localization of lymphoma, is the only diagnostic tool of PAL.

The HPS is a very rare and lethal disease; diagnosis is based on some criteria (Table 1). Acquired HPS in adults is associated with lymphoma in 35% of cases, mainly non-Hodgkin’s lymphoma [13]. To our knowledge, our case report of PAL revealed by HPS has not been reported in literature. We distinguish a primary HPS to designate an inappropriate immune response to viral infection leading to uncontrolled proliferation of benign histiocytes and secondary HPS (reactive), which is commonly associated with infectious diseases (46%), malignancy (29.7%), systemic diseases (7.2%) and no identified causes (18%) [14]. In immunocompetent patients, the first malignancy associated with HPS is T-cell lymphoma, especially when the trigger is identified as EBV [13].

The baseline staging (Physical examination, bone-marrow biopsy, the thoraco-abdominal CT scan and gastroscopy) must be realized to exclude other localisations and retain the diagnosis of PAL.

The treatment is based on chemotherapy. The role of radiation therapy and surgical excision of the adrenal glands are not known [1,13]. Because of the rarity of PAL, therapeutic regimens have not been defined in detail. Most patients with PAL have been treated with CHOP chemotherapy or MACOP-B chemotherapy (Methotrexate, folinic acid, Doxorubicine, Cyclophosphamide, Vincristine, Bleomycin and Prednisone). A recent study by Coiffier et al. [15] demonstrated that the addition of rituximab to CHOP (R-CHOP) increases significantly the rate of complete response and improves event-free and overall survival as compared with standard CHOP alone. Only two patients with bilateral PAL B-cell who achieved complete remission using R-CHOP chemotherapy were reported in the literature [1]. Our patient received Rituximab in complement of chemotherapy with complete response.

The prognosis of patients with PAL is very poor, although cases of complete remission were described. Survival in 1 year is exceptional [2,3]. Poor prognosis of PAL is thought to be due to the presence of HPS and adrenal insufficiency at the time of presentation requiring glucocorticoid replacement therapy [1,5,13].

4. Conclusion

This case raises the suggestion that HPS should be added to the modes of revelation of PAL. Then, abdominal CT scan or abdominal MRI should be considered in the investigation of an HPS with no identified etiology. In addition, it is important to underline the possibility of a normal first bone-marrow aspiration in HPS; so it is interesting to repeat this examination if there is a strong clinical suspicion. Currently, the scientific data about this association is nonexistent; other studies are necessary to improve the knowledge on this association.

Table 1

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<th>Diagnostic guidelines for hemophagocytic syndrome, from [16]. The diagnosis can be established by fulfilling five of the eight criteria.</th>
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<td>Critères diagnostiques du syndrome d’activation macrophagique, d’après [16].</td>
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Clinical criteria

- Fever (> 7 days)
- Splenomegaly

Laboratory criteria

- Bicytopenia without marrow hypoplasia, including:
  - Hemoglobin < 9 g/dL
  - Platelet count < 100000/mm³
  - Neutrophil count < 1000/mm³
- Hypertriglyceridemia ≥ 3 mmol/L and/or hypofibrinogenemia < 1.5 g/L
- Hyperferritinemia > 500 μg/L
- Increased soluble CD 25 levels > 2400 UI/ml
- Low/absent Natural Killer cell activity

Histological criteria

- Hemophagocytosis

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


