Non Hodgkin’s lymphoma involving the adrenal glands and the central nervous system (CNS): a particular evolution after chemotherapy


(1) Department of Endocrinology, Marc Linquette Clinic, 6, rue du Pr. Laguesse, CHRU de Lille, 59037 Lille.
(2) Department of Pathology, Eurasante Center 6, rue du Pr. Laguesse, CHRU de Lille, 59037 Lille.
(3) Department of hematology, Huriez Hospital, 6, rue du Pr. Laguesse, CHRU de Lille, 59037 Lille.

Reprint request: J.-L. Wémeau, address above.
e-mail : jl-wemeau@chru-lille.fr

INTRODUCTION

Endocrine glands involvements by non Hodgkin lymphoma (NHL) are less than 3% of extranodal presentation [9, 17]. Most of them reach the thyroid gland, since 2 to 10% of malignant tumors are lymphoma, with a peak incidence of the disease occurring around the seventh decade [8]. Lymphomas of the pituitary gland (25% of all diagnosis of malignant pituitary gland proliferation after histological observation) involve mainly the posterior pituitary gland with a peak incidence around 60 years [11]. Since 40 years, only few 70 cases of adrenal gland lymphoma were reported [1, 5, 6, 12, 15, 17, 24]. 25% of which were Diffuse Large B Cell Lymphoma (DLBCL) [18]. We report a new case of malignant NHL involving the central nervous system (CNS) and both adrenal glands, associated with a partial adrenal insufficiency and a dissociated therapeutic response.

CASE REPORT

A 51-year-old man was admitted to the hospital because of generalized seizures. The magnetic resonance imaging (MRI) images showed a cerebral mass suggesting a lymphoma
The stereotactic biopsy confirmed the diagnosis of malignant NHL with diffuse large B-cell lymphoma.

The abdominal computerized tomographic (CT) scan showed two large and homogeneous adrenal lesions (fig. 2a), which measured 5x1.5 cm on the right side and 4x4 cm on the left side. Physical examination showed no fever, not any sign of adrenal dysfunction, except a low blood pressure (about 70/50 mm Hg). Serum sodium level was 137 mEq per liter and potassium level 4.1 mEq per liter, without renal or liver dysfunction. Confirming the clinical suspicion of mild adrenal insufficiency, serum cortisol level was 8.8 µg/100 ml at 08:00 A.M (normal range: 9-22 µg/100 ml) with a high ACTH level about 294 pg/ml (normal range 10-50 pg/ml). There was a weak serum cortisol increase to 12.6 µg/100 ml, 60 min after the cosyntropin stimulation test (with 250 µg intramuscular injection). The FLU was in the normal range (43 µg/day, normal 20-110 µg/day, urine creatinine 1.22 g/day). The levels of 17-OH progesterone and 11 desoxycortisol were normal. Aldosterone concentration was normal in the laid position with a weak stimulation when standing up. Plasma renin activity was normal; nevertheless the urinary level of aldosterone by 24 hours was low. The androgen secretion was decreased (table I). The level of 24 hr urine catecholamine (on 3 days) and plasmatic level of chromogranin A were normal, ruling out the diagnosis of pheochromocytoma. After substitution with hydrocortisone, a CT scan directed needle biopsy of the...
adrenal mass was performed. Haematoxylin and eosin
stain showed sheets of large lymphoma cells with large
vesicular nuclei and prominent nucleoli. The immuno-
histochemical study revealed a distinct membrane stain-
ing for CD20 which confirmed the diagnosis of DLBCL
(fig. 3).
Except the adrenal and CNS involvement, there
was no extension of DLBCL. The patient received 2 cycles
of Methotrexate (MTX), Etoposide, BCNU, Prednisone
(MVBP) and 6 intrathecal MTX injections. An MRI ob-
tained six months after initial diagnosis, showed a reduc-
tion of the cerebral tumor (fig. 1b), while the adrenal
lesions paradoxically increased (fig. 2b) and measured at
that time 7 x 3.1 cm on the right and 4 x 6 cm on the left.

Clinical and radiological follow-up revealed after few
weeks, an epidural infiltration of the lymphoma. Intensive
chemotherapy was decided with Adriamycin, Cyclo-
phosphamide, Vindesine, Bleomycine, and Prednisone
(ACVBP) associated with intrathecal injection of MTX.
The patient gradually weakened because of the progres-
sion of the lymphoma with appearance of neurological
and visual disorders. A new MRI showed massive exten-
sion of the epidural and cerebral lesions. The patient was
still alive ten month after the intensive chemotherapy.
The patient died 16 months after initial diagnosis of
neurological progression.

DISCUSSION

This patient did not have any symptoms of adrenal in-
sufficiency but a biological mild glucocorticoid and
mineralocorticoid deficiency, and a decrease of andro-
genic secretion. The most surprising characteristic of this
observation was the decrease of the cerebral mass after
chemotherapy whereas the adrenal lesion paradoxically
increased. For this reason, the surgical biopsy was de-
cided, allowing the histological diagnosis.

Adrenal lymphoma is extremely rare. 73% of primary
adrenal lymphomas reported in the literature are bilateral
with a size ranging from 3 to 17 cm. Male to female ratio
is 2.2 to 1 and median age is 68 years [4, 15, 17, 25].

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<td>Mineralocorticoid and androgen function.</td>
<td>Fonction minéralocorticoïde et androgénique.</td>
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<td><strong>PRA (mg/ml/h)</strong></td>
<td><strong>Laid</strong> (N: 0.5-3)</td>
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<td><strong>Aldosterone (pg/ml)</strong></td>
<td>36 (N: 15-150)</td>
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<td><strong>Aldosterone in urine</strong></td>
<td>1.1 µg/day (N: 2.5-21.5)</td>
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### Androgen function
- **testosterone**: $2.97 \times 10^{-2}$ ng/dl (N: $3.510^{-2} - 9.510^{-2}$)
- **SBP**: 380 nmol/dl (N: 150-450)
- **DHA**: $1.42 \times 10^{-2}$ ng/dl (N: $1.5 \times 10^{-2} - 9 \times 10^{-2}$ ng/dl)
- **DHAS**: $12 \mu$mol per dl (N: 20-150 µmol/l).

**Figure 3a**: Hematoxylin and eosin stain: Diffuse proliferation of large lymphoma cells, with irregular cleaved nuclei and numerous mitoses (x200).
**Figure 3a** : Coloration à l’hématoxyline et à l’éosine. Prolifération diffuse de larges cellules lymphomateuses avec noyaux irréguliers et nombreuses mitoses (x 200).

**Figure 3b**: Immunohistochemical study: strong expression of CD20 by lymphoma cells (x200).
**Figure 3b** : Immunomarquage : forte expression du CD20 par les cellules lymphomateuses.
Nevertheless, adrenal DLBCL with adrenal insufficiency affects men more than women (ratio: 3/1). The reasons still remain unknown. The median of age is 67. There is no obvious difference between men and women, about the age of diagnosis, predictive factors, histological features, and prognosis. When lymphoma is diagnosed, prevalence of autoimmune diseases is 13% and infection by HIV is present in 4% [6]. Clinical symptoms of adrenal lymphomas include fever (46%), weight loss (24%), abdominal pain (26%) and symptoms of adrenal insufficiency. Nevertheless, some adrenal lymphomas remain asymptomatic [6, 16, 23, 25]. When adrenal gland is infiltrated, it’s crucial to rule out an adrenal insufficiency. Destruction of approximately 90% of the adrenal cortex is necessary before adrenal insufficiency becomes apparent [12, 17]. There would not be correlation between the size of the adrenal lesion and the degree of adrenal insufficiency which is more often partial and asymptomatic [6, 18, 25]. 36 to 75% of the patients with isolated adrenal lymphoma [6, 25] and 19% of patients with diffuse lymphoma involving the adrenal glands develop an adrenal insufficiency [12]. Primary adrenal insufficiency is described in two third of the patients which present a bilateral adrenal involvement. This situation is rare when DLBCL involves a unique adrenal gland. It rarely appears in the early stage of bilateral adrenal DLBCL [15] and generally occurs when the lymphoma is widespread [16, 18]. The biological analysis can detect elevated serum lactate dehydrogenase (LDH) level, increase of B2 microglobulin and calcium levels, inflammatory syndrome. Idiopathic thrombocytopenic purpura has been described [3].

Adrenal lymphoma can be discovered as incidentaloma when imaging investigation for non adrenal disorders is performed [19]. The prevalence of adrenal incidentaloma fluctuates between 1 and 5% [19, 21]. In the study of Barzon et al., 15% of the incidentalomas were bilateral. They found one case of adrenal lymphoma in a population of 202 adrenal incidentalomas (0.5%) [2]. 30% of adrenal incidentalomas are known to be metastases. In one third of these cases, the initial localization remains unknown [7]. The lymphoma has to be evocated especially for patients with a bilateral non functional incidentaloma. Several autopsies series have shown that 20-25% of patients with NHL have adrenal gland infiltration. When adrenal gland is involved, 30 to 40% of lymphomas correspond to DLBCL consisting in a diffuse large cells proliferation, which express specific antigens of B lymphocytes (CD20 and/or CD79a) [6]. In case of bilateral adrenal lesions, it is important to search for other localizations of NHL: CNS, gastrointestinal tract, lymphnode and other endocrine organs [6, 12, 16, 24]. CNS involvement has been reported to occur in 10-20% of patients with systemic lymphoma [27] and is associated with poor prognosis [12-14]. The most common site of CNS involvement is the leptomeninges and the cerebrum. The prognostic depends on clinical factors constituting the parameters of the international prognostic index (IPI) [10]. Several prognostic factors of DLBCL have been described: old age (more than 60 years), initial presentation with adrenal insufficiency, huge tumor size (more than 10cm), elevated serum LDH level and B2 microglobulin (more than 3mg/l), and involvement of other organs [15]. Death is the consequence of severe infection, pulmonary embolism or DLBCL progression [6, 16, 18]. According to Hollender et al., patients with CNS involvement at diagnosis, have a median survival of 5.4 months, 3.8 months when there is a relapse of CNS and 1.8 months when there is a progression of the disease [13]. When lymphoma is diffuse, intensive chemotherapy have to be start quickly. In case of leptomeninges and cerebrum involvement, a combination of radiotherapy and chemotherapy, based on high-dose of Methotrexate seems to be the most efficient therapy in terms of survival rates [12, 13, 20, 27]. Patients with widespread disease refractory to chemotherapy and recurrent adrenal insufficiency rarely survive longer than one year after diagnosis [15]. Yoshida and al precise that prophylactic treatment is successful when systemic lymphoma is controlled [27]. Treatment of DLBCL involving adrenal gland and CNS include current systemic chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) and prophylaxis with intrathecal chemotherapy with Methotrexate. Radiation therapy is generally less effective [12, 14, 20]. Promising results prompted clinical investigation with rituximab in chemotherapy for such aggressive form of B-cell DLBCL [22].

CONCLUSION

This observation confirms the importance of hormonal and morphological assessment when adrenal incidentaloma is found in the course of carcinological pathology. 1/ Adrenal insufficiency and pheochromocytoma should be excluded. 2/ Biopsy remains the most reliable diagnostic method in order to adapt treatment. 3/ DLBCL should be included in the differential diagnosis of bilateral adrenal masses. In this case, we have remarked the initial and dissociated response to chemotherapy on the cerebral and the adrenal lesions, which has been probably a sign of unfavorable prognosis and faster evolution of lymphoma. The effect of corticotherapy on cerebral edema can explain the decrease of CNS involvement without modification of adrenal lesions.
REFERENCES