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Diagnostic and therapeutic pitfalls in neurosarcoïdosis

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Abstract

Neurosarcoïdosis is a diagnostic challenge, especially in the absence of systemic involvement, even when cerebral biopsies show noncaseating granulomas. We report a patient with a pineal germinoma associated with an extensive peri- and intra-tumoural granulomatous reaction, who was first diagnosed as possible neurosarcoïdosis. A second patient was initially considered as suffering from Multiple Sclerosis. Brain biopsy showed typical granulomas and gallium scintigraphy revealed other locations of the disease. Unfortunately, he developed a severe, steroid-induced, epidural lipomatosis at the Th3-Th8 levels and died unexpectedly after surgical decompression.

Granulomatous inflammation in a tissue obtained by biopsy from a midline lesion should be always considered for the differential diagnosis of germinoma. Corticosteroid-sparing immunosuppressant drugs should be used early in neurosarcoïdosis.

Keywords: Neurosarcoïdosis; pineal germinoma; epidural lipomatosis; stereotactic biopsy.

Introduction

Sarcoïdosis is a multisystem granulomatous disease of unknown aetiology. Its pathology is characterised by the formation of multiple noncaseating granulomas which injury the tissues in which they occur. The process can be self-limiting or chronic, with episodic relapses and remissions. The most commonly affected organs are the lungs, skin and lymph nodes. Clinical involvement of the nervous system is present in about 5% of all patients during the whole course of the disease (Zajicek et al., 1999; Vinas and Rengachary, 2001; Hoitsma et al., 2004). However, post-mortem studies suggest that ante-mortem diagnosis is only made in 50% of cases with neurosarcoïdosis (NS) (Stern et al., 1985; Iwai et al., 1993). NS without systemic involvement is uncommon and difficult to identify, as the disease can mimic various neurological disorders as aseptic meningitis, meningoradiculitis, tumour or multiple sclerosis (MS) (Uchino et al., 2001). The definite diagnosis of NS is based on a positive nervous biopsy (Zajicek et al., 1999). However, even the histopathological analysis may be further obscured by the occurrence of either other primary granulomatous diseases or a secondary sarcoïd-like reaction (Nowak and Widenka, 2001).

Treatment of NS also remains a challenge. Most patients are treated with systemic corticosteroids, often initiated with bolus pulsed intravenous methylprednisolone followed by a prolonged oral therapy. Significant side-effects are frequent (Zajicek et al., 1999). In case of corticosteroid-resistant signs and symptoms, a short-course, pulse-dose regimen of cyclophosphamide has been advocated (Doty et al., 2003).

The two cases illustrated here, exemplify the diagnostic and therapeutic problems linked to NS. The first patient suffered from a pineal germinoma with a major granulomatous reaction within and surrounding the tumour, as previously reported in only 5 other cases in this peculiar location (Kraichoke et al., 1988; Nishibayashi et al., 2005; Moon et al., 2005). The second patient was first misdiagnosed as MS on the basis of bilateral optic neuritis and several lesions of the white matter with among them, two peri-callasol lesions. Definite diagnosis required a brain biopsy. He developed a compressive, corticosteroid-induced, epidural lipomatosis at the Th3 to Th8 levels, and died unexpectedly after surgical decompression.

Case n° 1. This 19-year-old man native of Portugal, complained of vertical diplopia, Parinaud’s syndrome and headache since December 2002. He had no relevant medical antecedent. In March 2003, brain MR examination revealed a pineal tumour spreading to thalami and the right posterior part of
the mesencephalon. The lesion was $20 \times 13 \times 18$ mm in size and enhanced after intravenous injection of gadolinium (Fig. 1A). A germinoma or a pinealoma was suspected. A methionine PET-scan confirmed the hypermetabolic activity of the lesion. A first stereotactic biopsy was performed in February 2003 but was unsuccessful, as only reactive gliosis was observed. A second biopsy was performed in March 2003, and was complicated by local bleeding without permanent sequelae. The histopathological examination revealed epithelioid cells forming noncaseating granulomas, and the presence of a single multinucleated giant cell. Specific stainings for fungi and mycobacteria were negative. The inflammatory infiltrate included predominantly CD3 positive T-cells and occasionally CD20 positive B-cells. Granuloma cells were CD68 positive and extensive. Imaging showed a regression of the hypermetabolic activity of the lesion. A first biopsy was performed in September 2006 and revealed CD117 positive cells immunostained by anti-PLAP but not by bHCG-Gantibodies (Fig. 2). The tumour was infiltrated by numerous small lymphocytes. A diagnosis of germinoma was retained. Chemotherapy (etoposide-cisplatin) was initiated followed by radiotherapy. The tumour volume decreased by 75% and remained stable at the most recent control (July 2008).

Case n° 2. In 2002, a 41-year-old man presented a decreased bilateral visual acuity over several days, more marked in the right side. He did not describe retro-orbital pain. Brain MRI showed a thick right optic nerve with slight contrast enhancement, and one periventricular and one callosal, contrast-enhanced, lesions. CSF examination was normal, with no oligoclonal IgG bands. A diagnosis of possible MS was considered. A pulse of IV methylprednisolone (1 g/day for 5 days) was given with good improvement of visual acuities: from 1/10 to 6/10 in the right eye and from 6/10 to 8/10 in the left eye. In June 2005, visual acuity felt down again bilaterally, but still more on the right side. Brain MR examination showed several supra-tentorial lesions, with annular contrast enhancement. Spinal cord examination was normal. A second CSF examination revealed a single IgG band and several oligoclonal free kappa chains, not present in the corresponding serum. High dose IV methylprednisolone was administered with slight improvement of the visual acuity, from 2/10 to 4/10 on the right eye and from 6/10 to 7/10 on the left eye. Pallor of the right optic disc was observed at ophthalmologic examination. In December 2005, a new worsening of the vision occurred again. Brain MRI remained unchanged. A third pulse of corticosteroids was administered without success. The patient was then referred to our institution in January 2006. The ophthalmological examination showed a right reactive mydriasis, a visual acuity of 0/10 on the right eye and 4/10 on the left eye, and an atrophic right papilla. Brain MR examination showed an infiltrative lesion of both optic nerves up to the chiasma, and two enhanced lesions within the parenchyma of both medial parietal areas close to
the splenium of the corpus callosum (Fig. 3A, B, C).

A third CSF examination showed a moderate elevation of the protein content at 51 mg/dL (normal range: 15-45 mg/dL), normal count cell and absence of oligoclonal IgG bands. The serum angiotensin-

converting enzyme and calcaemia were not elevated, in contrast to the lysozyme level (15.9 mg/dL; normal range: 5-8 mg/dL). Chest computed tomography revealed multiple mediastinal nodes, and micronodular parenchymatous and subpleural infiltration.
compatible with pulmonary sarcoidosis. The gallium 67 scintigraphy showed abnormal uptake in submandibular, axillar and mediastinal nodes, and diffusely in the lungs. A bronchoalveolar washing indicated an increased CD4+/CD8+ T lymphocyte ratio and absence of fungi or mycobacteria. The bronchial biopsy did not show granulomas. A brain stereotactic biopsy demonstrated the presence of non caseating perivascular microgranulomas. The CD1a and CD20 surface antigens were not detectable, but CD3- and CD68-positive cells were present (Fig. 4A and B). A pulse of high dose IV methylprednisolone was given in February 2006, followed by IV cyclophosphamide (700 mg/m²/month) and oral methylprednisolone (0.9 mg/kg/day). After three courses of cyclophosphamide, MRI showed complete remission of intraparenchymal lesions and only a slight persistent enhancement of the pre-chiasmatic part of the right optic nerve (Fig. 3D, E, F). Unfortunately, the patient developed a subacute severe paraparesis in August 2006 due to an extensive epidural lipomatosis with compression of the spinal cord from Th3 to Th8 (Fig. 5). A decompressive laminectomy was performed, but the patient died suddenly two days later. Necropsy was performed, but the cause of death was not detected. The only systemic abnormality was the presence of several, partly calcified, fibrotic nodules of 1 to 7 mm in diameter in both lungs. The neuropathological examination revealed a fibrous granuloma containing some inflammatory cells and a single multinucleated cell surrounding the right optic nerve (Fig. 4C and E). Within both optic nerves, small, non-caseous, granulomatous foci were also present. Similar findings were observed in the callosal region that also affected the nearby medial parietal cortex (Fig. 4D and F). The spinal cord was free of any inflammatory or ischaemic lesion. The epidural mass contained only mature adipocytes surrounded by macrophages (Fig. 4G).

**Discussion**

These two cases stress the difficulty to establish a correct and early diagnosis of neurosarcoïdosis, even based on histological examination. A secondary sarcoid-like reaction may indeed be observed in a peri-tumoural process or in presence of foreign bodies. In addition to NS, other primary granulomatous diseases have to be considered: infectious (tu-
Our first patient illustrates the extensive sarcoïd-like granulomatous reaction induced by pineal germinoma. Only four cases of pineal neurosarcoïdosis have been reported so far, but two could be questioned. Saltzman (1958) reported one patient with partial resection of a pineal process presenting histopathological characteristics of sarcoïdosis. A second case (Schaefer et al., 1977) underwent a complete resection of a pineal tumour for which the histological diagnosis was sarcoïdosis. The third patient had a medical history of sarcoïdosis (Wall et al., 1985). Brain CT scan was performed because of change in mental status and revealed pineal and supra-sellar space-occupying lesions. Treatment with steroids lead to regression of these lesions. The patient died of cardiac arrest and autopsy confirmed the widespread presence of non-caseating granulomas in the brain and leptomeninges. The fourth case...
Fig. 4. — A: HE section of stereotatic biopsy revealed spongiosis, reactive gliosis and lymphocytic infiltrate that was predominantly located around and into vessels (B).
C: At post-mortem examination, a lesion ensheathing the optic nerve (arrows) appeared collagenized with few remnant lymphocytes and a giant cell (E, arrow). Similar findings were observed in the callosal lesion that also affected the nearby cortex (D, arrow and F).
G: Mature adipocytes, sometimes surrounded by macrophages, were observed in the epidural mass at the Th5 level.
had a open biopsy and was treated with corticosteroids and radiotherapy (Martin et al., 1989). Obviously, the first and the last cases must be cautiously considered, as a sarcoïd-like peritumoural reaction has been not fully excluded because of partial resections.

The occurrence of such sarcoïd-like reaction induced by intracranial germinomas is now well recognized, whatever the localization of the tumour (Bjornsson et al., 1985; Mueller et al., 2007). In a series of 18 germinomas, 5 were characterized by predominant fibrous and granulomatous tissue containing sparse neoplastic cells (type B) (Utsuki et al., 2006). This “type B” pattern was different of the more frequent “type A” pattern, consisting in large neoplastic cells infiltrated by small lymphocytes.

![Fig. 5. — Unenhanced T1-weighted spinal MR image in midsagittal plane at thoraco-lumbar level showing fatal drawbacks of prolonged corticoid therapy i.e. multiple vertebral body collapses due to steroid-induced bone weakening and expanding posterior epidural lipomatosis impinging on the spinal cord (arrows).](image)

Only five type B pineal germinomas have been reported so far (Kraichoke et al., 1988; Nishibayashi et al., 2005; Moon et al., 2005) in five young male patients (17, 19, 20, 22 and 22-year-old), with a similar clinical pattern at disease onset to our 19-year-old male patient. In the six cases, the area of inflammation always occupied the major part of the biopsy sample. Stereotactic biopsy led to the correct diagnosis in only one case, while further biopsies or direct surgery were needed in the other cases. The presence of plasma cells may explain the appearance of oligoclonal IgG bands in the CSF. The protooncogene C-kit (CD117) is known to be diffusely positive on the cell surface of germinoma and may be a more reliable tumour marker for intracranial germinoma than other markers such as PLAP (Nakamura et al., 2005). It should be noted that type B germinomas require up to 12 months to show complete enhancing mass resolution after radiotherapy, whereas type A tumours may disappear within one month of treatment (Utsuki et al., 2006). In contrast, spontaneous regression or remission of primary intracranial germinoma, as observed in our patient in June 2003, is exceedingly rare and to our knowledge, had been reported so far in only two patients (Ide et al., 1997; Murai et al., 2000).

Due to some similar neuroradiological findings and fluctuating symptoms, NS and MS are sometimes difficult to distinguish from each other. In a patient known with systemic sarcoïdosis, any neurological sign or symptom should be first considered as due to NS, the possible co-existence of sarcoïdosis and MS having to be excluded by brain biopsy. However, in a very recent series of 30 NS patients (Joseph and Scolding, 2009), 70% presented with initial neurological features, 23% had previous systemic features of sarcoïdosis, and 7% had simultaneous neurological and systemic signs and/or symptoms. Optic nerve disease at presentation of NS is observed in 30% to 38% of patients (Zajicek et al., 1999; Joseph and Scolding, 2009), and is bilateral in one third of the cases. Although optic neuritis is also a frequent presenting symptom of MS, a bilateral involvement is rare (5%) (McDonald and Bates, 1992). Callosal lesions are not specific for MS and may be also observed in NS and typically in Susac’s syndrome (Snyers et al., 2006). However, a MRI meningeal enhancement and/or the persistence of enhancing lesions of more than three months’duration are strong arguments against a diagnosis of MS.

CSF-restricted oligoclonal IgG bands are present in both disorders, more frequently in MS (up to 95% of cases) than in NS (< 50%) (Sindic et al. 2001). Oligoclonal free kappa bands are also indicators for
an intrathecal immune reaction without specificity for a given disease (Goffette et al. 2004). Although these bands are persistent over the course of the disease in MS, they may disappear in treated NS. In addition, the presence of CSF-specific oligoclonal IgG in NS is associated with a high protein level not generally observed in MS (Joseph and Scolding, 2009). These clinical, MRI and CSF abnormalities should alert the clinician for the search of systemic sarcoidosis by appropriate tests (chest X-ray, chest computerized tomography, broncho-alveolar lavage, gallium scan, serum angiotensin converting enzyme level, ophthalmological examination). In case of positive results, a suitable site of biopsy could be chosen (lymph nodes, liver, lung, skin). In case of negative results, a nervous system biopsy guided by 3D MRI scans should be performed, if possible, in order to obtain a definite diagnosis of NS.

The diagnosis of NS is thus “definite” in our second patient, because of the presence of a positive nervous system histology associated with signs and symptoms of generalized sarcoidosis (Zajicek et al., 1999). The very low visual acuity and the risk of complete blindness lead us to start an aggressive treatment combining corticosteroids and cyclophosphamide (Doty et al., 2003; Scott et al., 2007). MRI lesions disappeared after three courses of immuno-suppressive drug. Unfortunately, the patient developed over 6 months severe, corticosteroids-induced, side effects, with Cushingoid face, and extensive epidural lipomatosis. The latter was the cause of a subacute paraparesis requiring a surgical decompression. Although the surgical procedure of laminectomy itself carries relatively low risk, the postoperative mortality of these patients is rather high, up to 22%, due to an immunocompromised state and altered general health status (Fessler et al., 1992).

In conclusion, granulomatous inflammation in a tissue obtained by biopsy from a midline lesion should always be considered for the differential diagnosis of germinoma. Corticosteroid-sparing immunosuppressant or immunomodulatory drugs should be used early in patients with NS. They may consist either in methotrexate (10-25 mg once weekly, combined with folic acid, 1 mg/day), ciclosporin (50 mg three times daily), cyclophosphamide (50-200 mg daily, or 500 mg intravenously, every 2-3 weeks), or in hydroxychloroquine (200 mg/day) (Hoitsma et al., 2004). Refractory forms of NS could be also treated with anti-TNF α products, like infliximab (5 mg/kg once, at week 0, 2, 6, and then every 8 weeks over several months) (Ritzenhaler et al., 2009).

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