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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 a 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.*

*Key words*: 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 antemortem 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-callosal 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 × 13 × 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 CD68 positive microglial activation was present. Immunostainings for placental alkaline phosphatase (PLAP), P53, vimentine, glial fibrillary acidic protein and Ki67 were negative. These results supported either a primary granulomatous process or a sarcoid-like reaction adjacent to a tumour process, although no tumoural cells were observed in the biopsy sample. Chest computed tomography was normal as well as blood and CSF analysis. Because of *spontaneous* clinical improvement, and simultaneous *disappearance* of the brain MRI lesion three months later (June 2003), no treatment was proposed (Fig. 1B). Until 2005, the patient felt better with remission of headache, and decrease of diplopia. He wore corrective glasses with prisms. In the meantime, consecutive brains MRI revealed a waxing and waning space-occupying lesion (Fig. 1A, B, C). In May 2005, the patient abruptly presented intense early morning headache and vertical double vision in all direction of gaze, predominant to the right. A right extension of the lesion (Fig. 1D), with contrast enhancement, was demonstrated on MR scans. A new methionin PET-scan showed a regression of the pineal hypermetabolic activity, but its extension to both thalami predominantly in the right side. The patient was therefore referred to the Department of Neurology for treatment of possible isolated NS. The serum levels of angiotensin-converting enzyme (37.5 IU/L; normal range: 5-18 IU/L) and lysozyme (23.2 mg/L; normal range: 5-18 mg/L) were slightly elevated; βHCG level was normal. CSF examination revealed a normal cell count and protein content, absence of neoplastic cells but several oligoclonal IgG bands not present in the matched serum. Chest computed tomography was again normal. The gallium 67 scintigraphy showed no increasing uptake area. After an intra-venous pulse treatment with methylprednisolone (1 g/day for 5 days), oral methylprednisolone (0.6 mg/kg) was chronically maintained, with good resolution of headache, and mild improvement of diplopia and of the Parinaud's syndrome. Because of corticosteroids side effects, intravenous cyclophosphamide infusions were started (700 mg/m²/month) with a reduced dosage of methylprednisolone (32 mg per day). In August 2006, after five infusions of cyclophosphamide, headache worsened due to the extension of the space-occupying lesion and development of hydrocephaly (Fig. 1E-F). A third biopsy was performed in September 2006 and revealed CD117 positive cells immunostained by anti-PLAP but not by βHC-Gantibodies (Fig. 2). The tumour was infiltrated by numerous small lymphocytes. A diagnosis of germinoma was retained. Chemotherapy (etoposide-cisplatine) 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-tentoriel 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

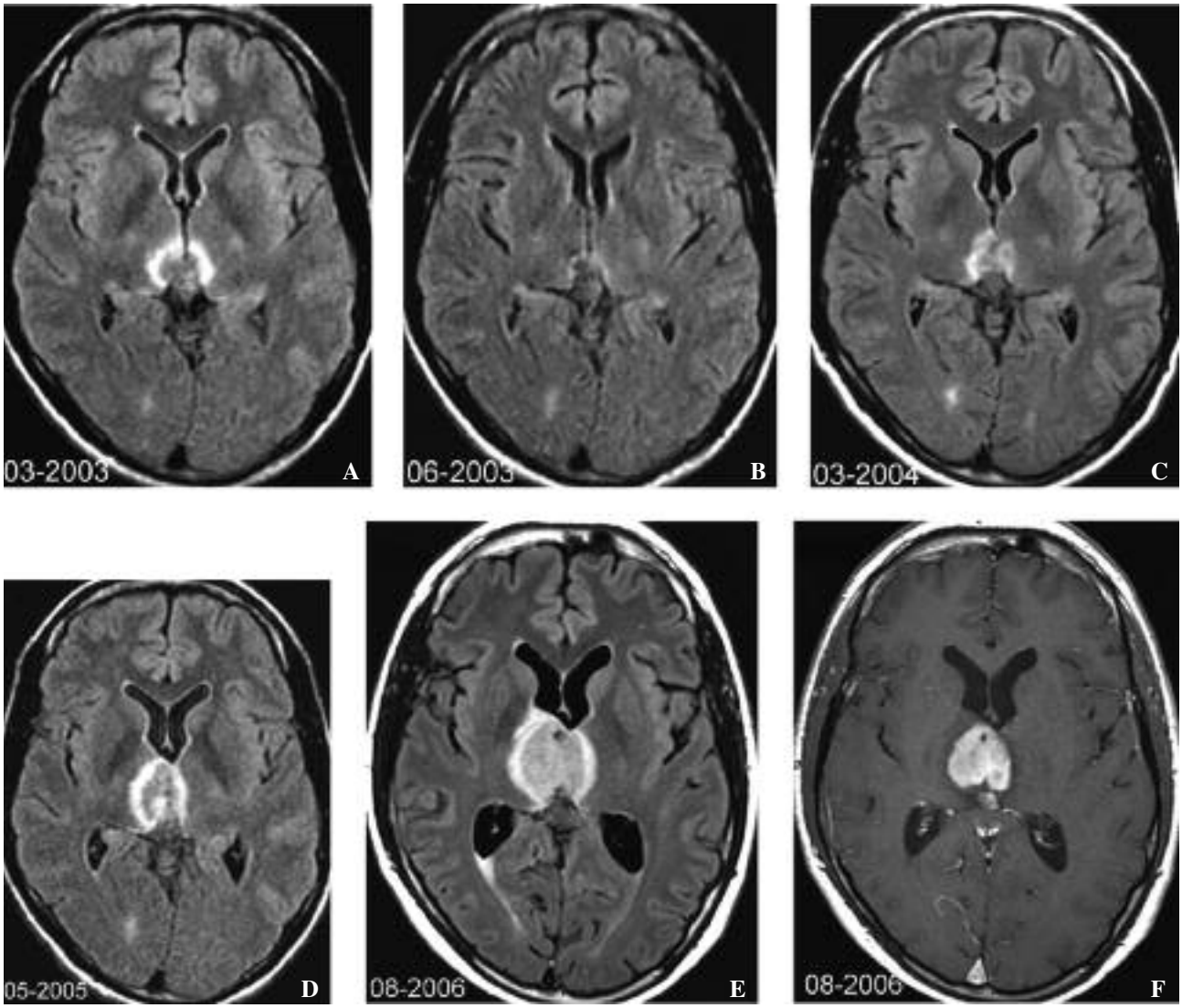


FIG. 1. — Pre-treatment brain MR images of patient #1.

1A-1E: Serial unenhanced Fluid-Attenuated inversion recovery (FLAIR) images in a similar slice location monitoring from March 2003 to August 2006; 1F: post-contrast T1-weighted image in August 2006.

1A. March 2003: a ring-like abnormal hypersignal intensity of 27 mm in full maximal diameter centred on epiphyseal area and impinging symmetrically on medial aspects of the thalami was present.

1B. June 2003: brain status had completely normalized.

1C. March 2004: an epiphyseal lesion of 21 mm in diameter with similar features to those observed 12 months previously (1A) had reappeared.

1D & 1E. May 2005 and August 2006: progressive increase in size with time of the tumoral process was obvious. Observe clear delineation between central homogeneous less hyperintense tumoral area and peripheral edematous more hyperintense ring. Slight increase in ventricular size and beginning per-ependymal transudation due to obstructive hydrocephalus had appeared on the last examination (August 2006).

1F. August 2006: post-contrast T1-weighted image in similar slice location as previous views demonstrated intense and homogeneous contrast-enhancement of sharply delineated central tumoral area. In turn, hypointense edematous ring failed to enhance.

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

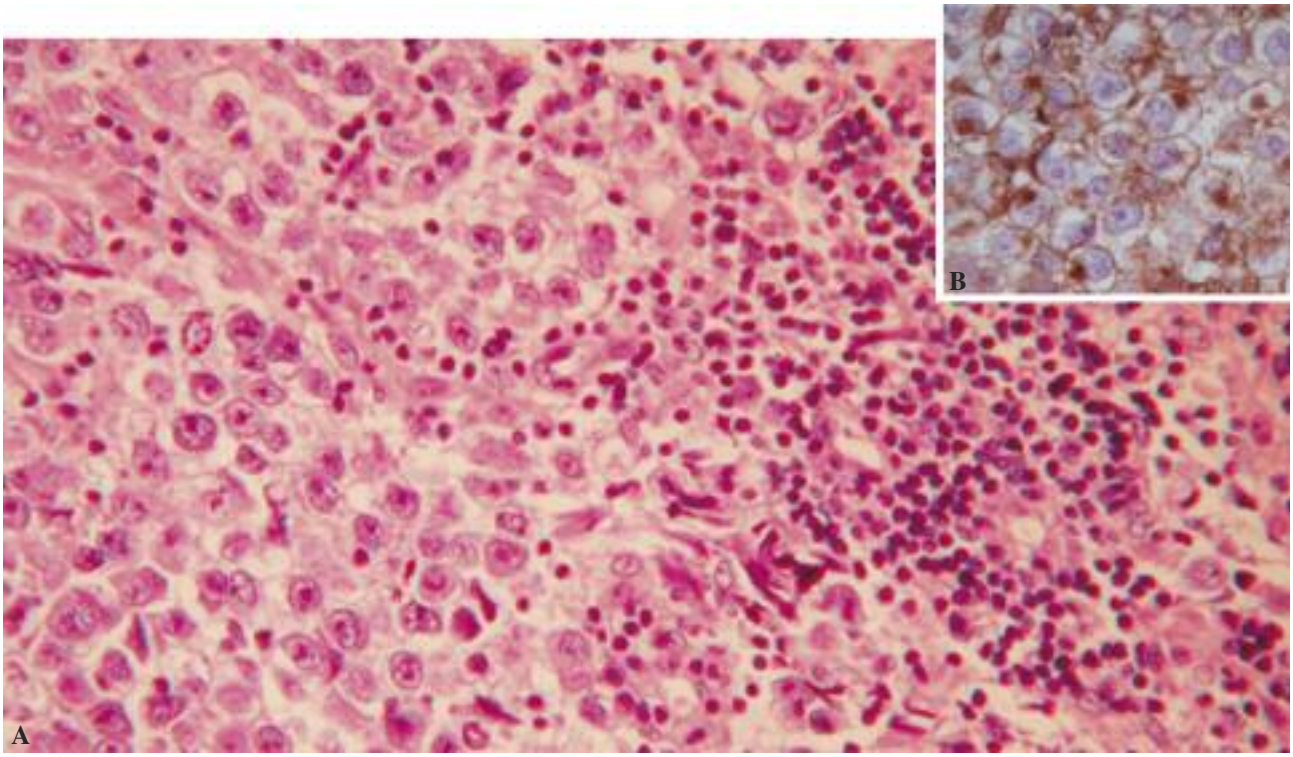


FIG. 2. — A: HE section of the third biopsy revealed a tumor constituted of lobules of cells with clear cytoplasm, rond nuclei and well-defined cell borders. A lymphoïd infiltrate is present on the right. B: Antibodies to placental alkaline phosphatase stain membranes of tumoural cells.

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 sarcoïd-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-

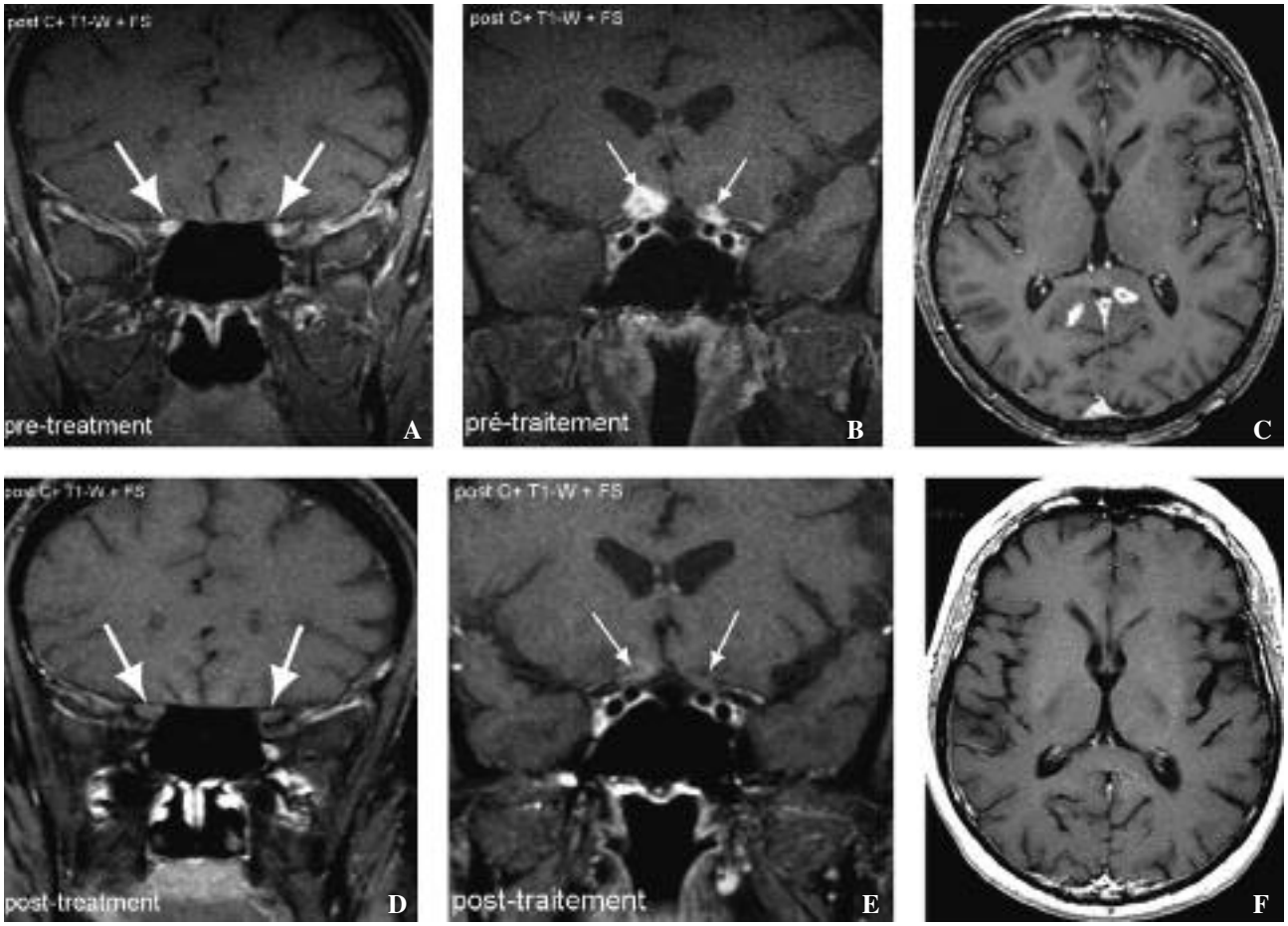


FIG. 3. — Comparative pre- and post-treatment cranial MR images of patient #2.

3A-C: pre-treatment contrast-enhanced T1-weighted images.

3D-E: post-treatment contrast-enhanced T1-weighted images corresponding to 3A-C.

3A: frontal view with fat suppression option showing swelling and contrast-enhancement of both optic nerves near the entry of the optic canal (arrows).

3B: similar frontal view in a slightly more posterior plane showing swelling and contrast-enhancement of pre-chiasmatic segments of both optic nerves (arrows), mainly on the right side.

3C: transverse view showing two enhanced foci within the parenchyma of both medial parietal areas near the splenium of the corpus callosum.

3D: view in a similar slice location as 3A showing post-treatment complete normalization of anterior optic nerve status at this level.

3E: view in a similar slice location as 3B showing post-treatment complete disappearance of pre-chiasmatic left optic nerve abnormalities but only partial regression of right sided ones.

3F: view in a similar slice location as 3C showed complete and bilateral disappearance of parenchymal lesions.

berculosis, fungi, syphilis), tumoural (lymphoma), inflammatory (Wegener's granulomatosis, granulomatous angiitis, Langerhans cell histiocytosis) (Nowak and Widenka, 2001).

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

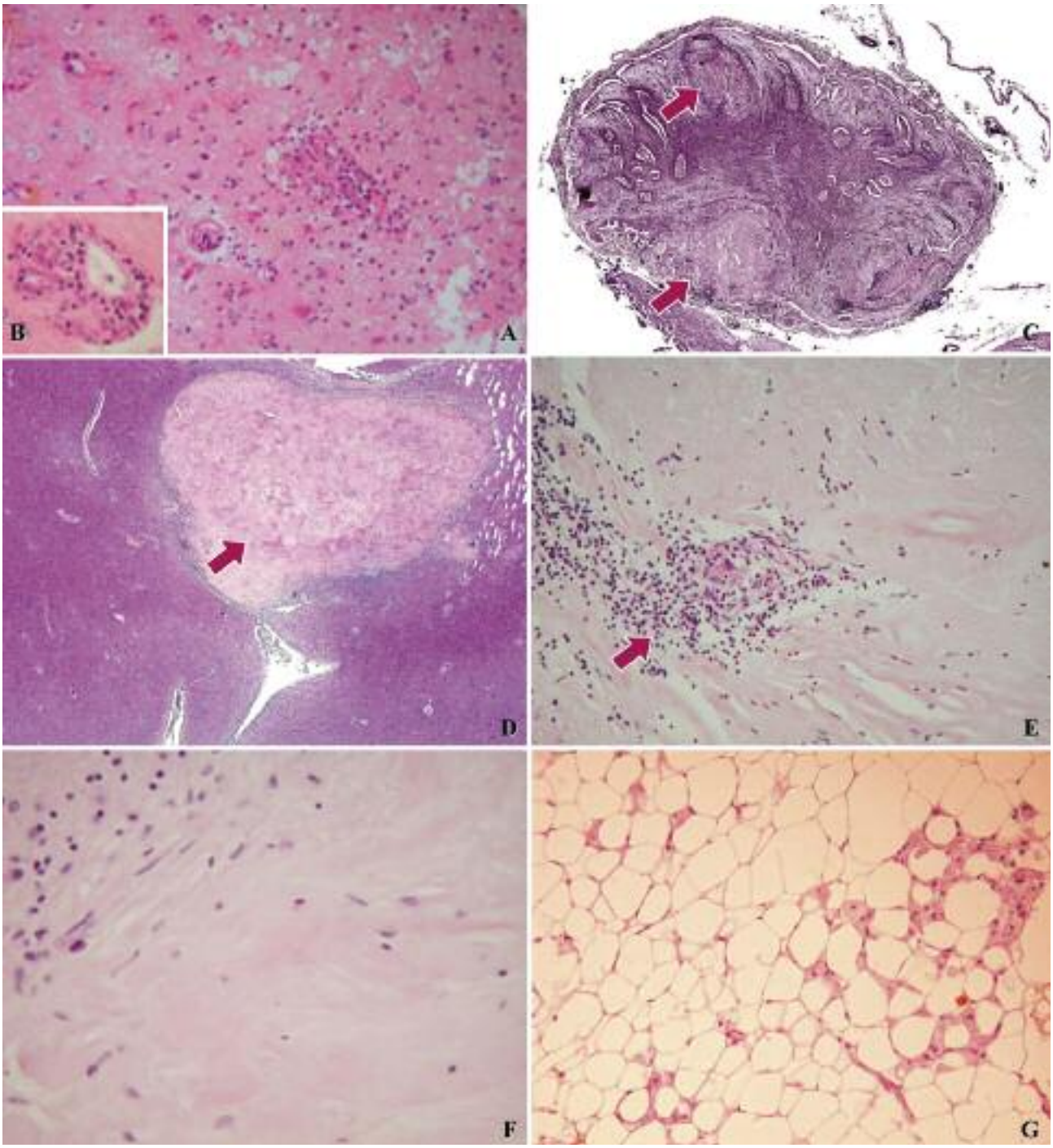


FIG. 4. — A: HE section of stereotatic biopsy revealed spongiosis, reactive gliosis and lymphocytic infiltrate that was predominantly located around and into vessels (B).

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.

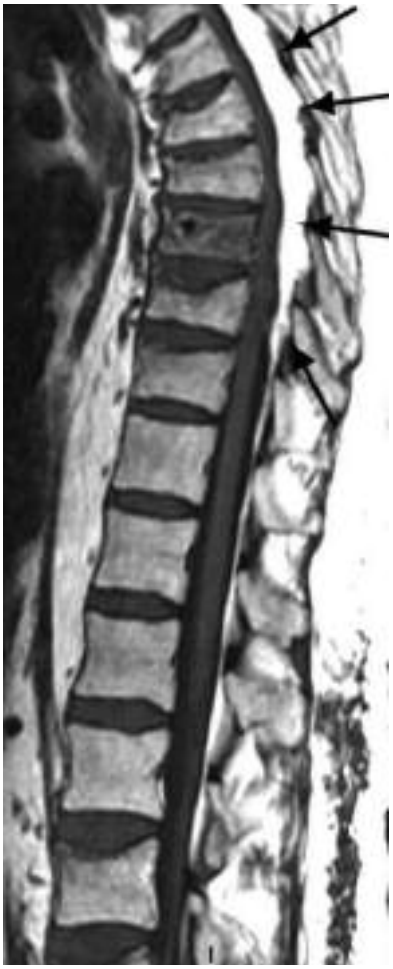

FIG. 5. — Unenhanced T1-weighted spinal MR image in mid-sagittal plane at thoraco-lumbar level showing fatal drawbacks of prolonged corticoid therapy i.e. multiple vertebral body collapses due to steroid-induced bone weakening and expanding posterior epidural lipomatosis impinging on the spinal cord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

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.

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 proto-oncogene C-kit (CD 117) 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 sarcoïdosis 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 sarcoïdosis (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 immunosuppressive drug. Unfortunately, the patient developed over 6 months severe, corticosteroids-induced, side effects, with Cushingoïd 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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