MENINGEAL CARCINOMATOSIS IN A CASE OF MALIGNANT MELANOMA MIMICKING TUBERCULOUS MENINGITIS

Cristina Tiu, Enache Delia, D. Vizitiu, Alina Florescu
Department of Neurology, University Hospital, Bucharest, Romania

ABSTRACT

The author report a case of a 39 year old man, with a history of malignant melanoma, who was hospitalised for papilledema, headache, diplopia and low fever, with progressive aggravation and death; the case particularities are the presence of papilledema due to a spinal cord compression and the differential diagnosis with tuberculous meningitis in a immunosuppressed patient.
Key words: malignant melanoma, tuberculous meningitis, spinal cord compression, meningeal carcinomatosis

We report the case of a 39-year-old male patient who was referred to the hospital for headache, diplopia, low-grade fever, and papilledema.

Medical history: malignant melanoma on his right side of torax (2001) complicated with right axillary lymph node metastasis (2003). Since 2003 the patient was treated with 2 chemotherapy courses each year and regular oncological evaluation (blood analysis, dermatological exam, chest X-ray, abdominal ecography and melanuria). He was considered disease free.

The debut was almost one month before with headache. He was investigated with brain MRI (normal aspect) and suboccipital puncture (normal aspect of the CSF). He received corticotherapy with a good outcome but the symptoms relapsed in 2 weeks.

Clinical examination revealed a low-grade fever patient, no adenopathy, no visceromegaly, with normal skin and mucous membrane. The neurologic examination showed diplopia, due to bilateral sixth nerve palsy, no meningeal signs, with signs of intracranial hypertension (the ophthalmoscopic examination revealed bilateral papilledema, venous engorgement and peripapillary hemorrhages.

The brain MRI (Figure 1) showed no significant hydrocephalia and focal growth involving the leptomeninges bilateral frontoparietal hyperintense FLAIR and T1 contrast enhancement and uptake of contrast agents; conclusion: active meningeal inflammation, no significant hydrocephalia, no intracerebral mass.

In spite of the presence of an intracranial hypertension, we decided to perform a lumbar puncture since the brain MRI didn't show an intracranial mass. The results: high CSF opening pressure 700 millimeters (mm) water, a high CSF xanthochromia, high range of CSF protein content –1371 mg/dl (normal

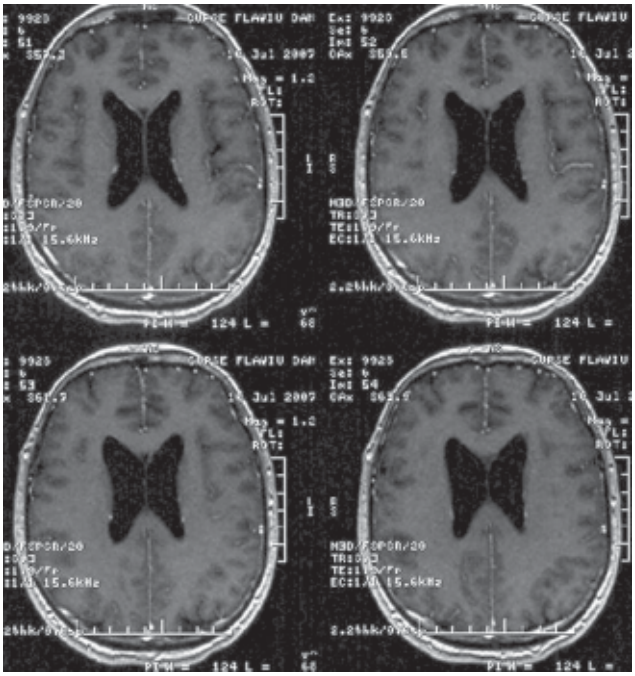

Figure 1
Brain MRI with normal aspect of the ventricles and leptomeningeal enhancement

15-45 mg/dl), low glucose content in the CSF 60 mg/dl (in blood – 146 mg/dl), cell counts – 34 and RBCs – 3040; flow cytometry – no evidence for atypical cell.

Lumbar puncture results, high range of CSF protein content and spontaneous coagulation suggest the diagnosis of Nonne-Froin syndrome. Characteristic for Nonne-Froin syndrome is the increased amount of exudative products found in the CSF below the level of a partial or complete subarachnoidal block of the spinal canal. We concluded that it was necessary an spinal lumbosacral MRI examination (Figure 2 and 3), which showed: diffuse thickening, patchy nodular

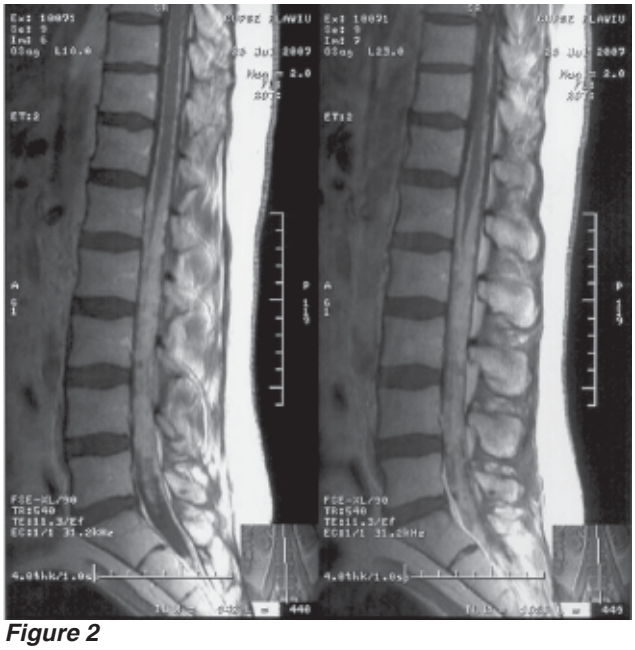

Figure 2
Sagital spinal cord view: leptomeningeal thickening, with nodules and spinal block

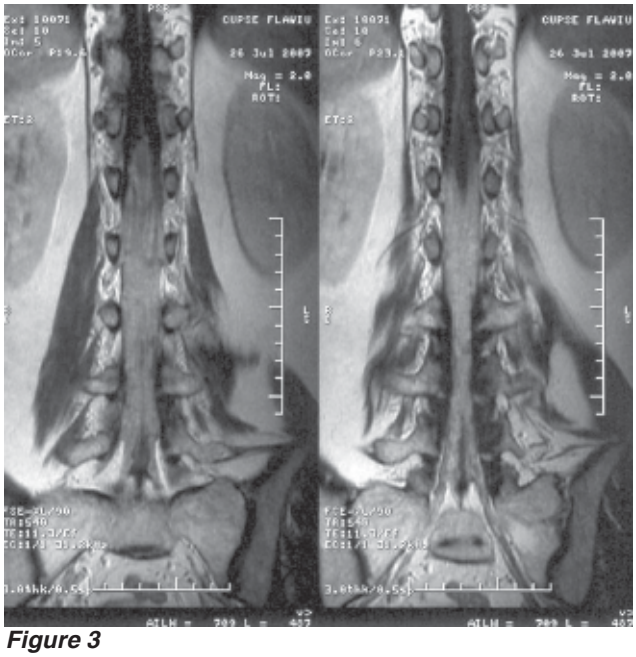

Figure 3
Coronal MRI of the cauda equina, with chronic infiltrative meningitis and spinal block

of the leptomeninge from conus medullaris and cauda equina root, with contrast enhancement; only fine loading with contrast agents of thoracic spinal cord pial vessel; obliterated lumbosacral subarachnoidal space. The images described at spinal cord MRI and MRI scan of the brain oriented medical diagnosis to infiltrative chronic meningitis with lumbar spinal block. Nonne-Froin syndrome was first described by Georges Froin in 1903 and Max Nonne in 1910, who concluded that xanthochromia and coagulation on the lumbar puncture's needle could be attributed to meningeal irritation and to fibrynogen presence (12, 13). Raven in 1912 attributed the Nonne's syndrome to a certain clinical condition, namely to the lumbosacral spinal cord tumor but frequently tuberculous meningitis and meningeal carcinomatosis can be the underlying cause (10). The following tests have been effectuated next: gram stain and Ziehl-Nielsen stain from CSF, culture of Mycobacterium tuberculosis in the CSF – negative; Melanuria was negative; PCR for Mycobacterium tuberculosis in CSF was positive.

Based on the positive PCR for mycobacterium tuberculosis, tuberculostatic treatment for tuberculosis meningitis was started. The patient evolution under treatment was aggravating, after 1 month from the moment that he was hospitalised he presented: tetraparesis with predominance of paraparesis who become quickly paraplegia with all the clinical signs of a complete cauda equina syndrome. Subsequently, obvious signs of cranial nerves lesions have been observed: bilateral deafness, bilateral mydriasis with anisocoria (L&R), meningeal syndrome (nuchal rigidity, aggravated headache), not responding to opioid medication, changes in mental status (somnolence, obnubilation) followed by epileptic left focal motor seizures with secondary generalization. Patient was subjected again to a MRI scan of the brain which showed tetraventricular hydrocephalia and pathological signs of cortico-subcortical hyperintensity in both cerebellar hemispheres, compatible with the diagnosis of a paraneoplastic cerebellitis (Figure 4 and 5).

At family request, the patient was discharged from the hospital and deceased two weeks later (no autopsy results available).

DISSCUSSIONS

The case raised some problems of differential diagnosis. First, it was the presence of a papilledema and signs of intracranial hypertension with a normal brain MRI and a normal CSF examination.

The possible explanation for the normal CSF is the fact that the spinal tap was performed suboccipital and the gradient of proteins was lower at this level. Second, we were confronted with an intracranial hypertension syndrome without an obvious cerebral cause, only indirect signs of a chronic meningeal inflammation.

Third, we had a patient with spinal cord compression and a CSF examination that could fit both the diagnosis of meningeal carcinomatosis and tuberculous meningitis. Taking into account the fact that tuberculous meningitis is rapidly evolving with lethal prognosis in the absence of the treatment and sustained by the positive PCR for mycobacterium tuberculosis in the CSF we started the tuberculostatic drugs (four drugs regimen). The negative response of the patient

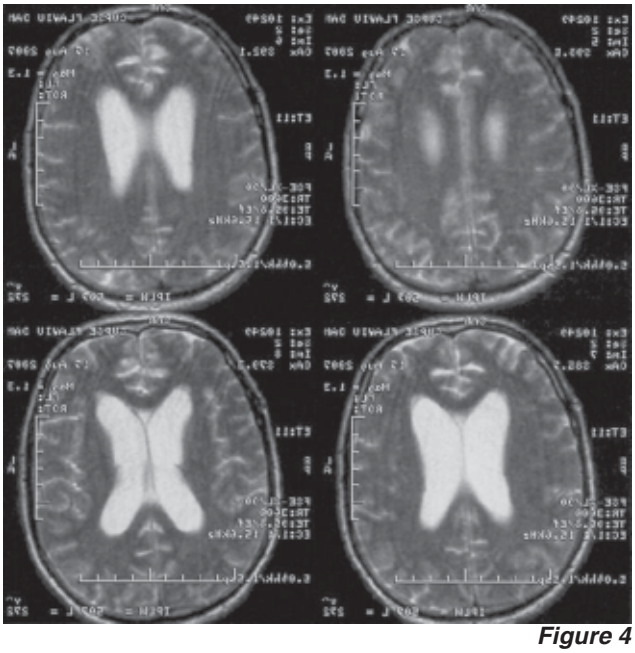

Figure 4
Cranial MRI with hydrocephalia

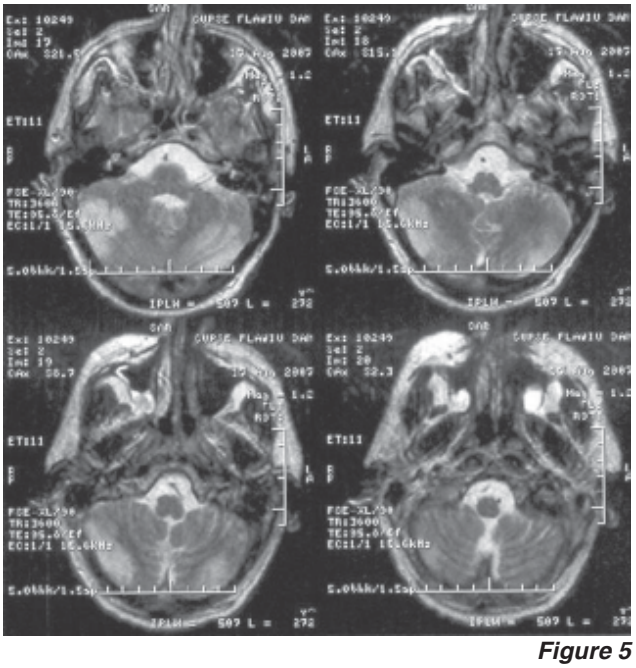

Figure 5
Hyperintense T2 lesions in both cerebellar hemispheres suggesting paraneoplastic cerebellitis

with progressive aggravation favored the diagnosis of meningeal carcinomatosis (usually tuberculous meningitis is rapidly improving under treatment). Although the PCR is considered a highly specific diagnostic tool there are papers that found the specificity to be 56% for CSF-PCR tests for M. tuberculosis (1). Another possible explanation is the cross-contamining of the CSF specimen with Mycobacterium fortuitum in the lab (an ubiquitous mycobacterium).

Yet, we can also think at the possible association of a tuberculous meningitis in an immunecompromised patient who also had leptomeningeal carcinomatosis from a malignant melanoma.

The following clinical evidence is in favor of meningeal carcinomatosis: polichemotreated melanoma with lymphatic metastasis, the negative response to the tuberculostatic medication, spreading of the meningoradicular signs (cauda equine syndrome, cranial nerve signs), associated with intracranial hypertension syndrome, vigility disturbances, the image of meningeal infiltration on MRI scan of the brain and spinal cord, the appearance of CSF, pathological signs of cortico-subcortical hyperintensity in both cerebellar hemispheres and finally the high level metastatic potential of melanoma.

Neoplastic meningitis (also called carcinomatous meningitis) is an important category, about 5% of patients with extraneural cancer have spread of malignant cells to the meningeal space. In 5% to 10% of patients it is the first clinical manifestation and in 20% it may develop after a prolonged disease free interval (1,2,6). This interval can be particularly large in the malignant melanoma (up to 10-15 years or more) (2).

Cancer cells reach the meninges by several routes:

1. hematogenous spread through the venous plexus of Batson, choroids plexus or meningeal arteries;
2. direct extension from contiguous tumor deposits;
3. invasion along perineural or perivascular spaces and 4) following spillage of malignant cells of a primary brain tumor into the meninges especially after partial surgical resection.

The cells spread via CSF flow and gravity, thus the most common sites of pathological involvement are the base of spine (basilar cisterns or posterior fossa) and the lumbosacral (cauda equina) (3).

Statistically, the more common cancer types seen in neoplastic meningitis are: breast, lung, malignant melanoma, and leukemia (4, 5). Regarding the metastasis of a melanoma, brain metastasis occurs in 39-54% of the cases and are considered a more aggressive form of disease (M3 stage disease) with a worse prognosis (6).

Clinical signs and symptoms depend on the tumor location and whether the metastases are causing hydrocephalus that develops from obstruction of CSF pathways at the level of the fourth ventricle, basal cisterns and tentorial openings or cerebral convexities (5, 7).

Leptomeningeal metastases are often suspected but not diagnosed by abnormal findings on cranial and lumbosacral spine neuroimaging. Cranial enhanced CT is abnormal in 25% to 50% of patients but MRI with gadolinium in over 75% (5, 8). Identification of malignant cells on cytological examination of CSF or by meningeal biopsy establishes a firm diagnosis.

Unfortunately, negative CSF cytology in cases of proven neoplastic meningitis ranges from 25% to 40%. In patients with negative CSF cytology, the diagnosis comes more frequently from biopsy of an MRI or CT enhancing meningeal site with subsequent histological examination (9).

We must point out that tetraventricular hydrocephalia is the result of excessive proteic exudation from Nonne-Froin syndrome which has the same CSF appearance as the intracranial hypertension syndrome, the primary diagnosis of the patient at the hospital admission; it should be further discussed if the VI bilateral palsy was secondary to the intracranial hypertension syndrome or was the result of actual meningeal infiltration but the clinical aspect with the involvement of other cranial nerves favor the carcinomatous infiltration of the nerves. Another element that sustains the diagnosis of carcinomatosis is the presence of the hypertintensities in the cerebellum.

CONCLUSION

The final clinical diagnosis was meningeal carcinomatosis from a malignant melanoma with a false positive result of the PCR for mycobacterium tuberculosis.

REFERENCES

1. **Pai M, Flores LL, Pai N et al** – Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis*, 2003; 3: 633-643.
2. **Dan Jinga** – Melanomul malign, 2003; 3: 33-35.
3. **Chamberlain MC** – New approaches to and current treatment of leptomeningeal metastasis. *Curr Opin Neurol*, 1994; 7: 492-500.
4. **Ellner JJ, Bennett JE** – Chronic meningitis. *Medicine*, 1976; 55: 341-369.
5. **Kim L, Glantz MJ** – Neoplastic meningitis. *Curr Treat Options Oncol*, 2001; 2: 517-527.
6. **Raymond L** – Barnhill: *Pathology of Melanocytic Nevi and Malignant melanoma*. Second edition, 2004: 357-358.
7. **Chamberlain MC** – *Neoplastic J Clin Oncol*, 2005; 23: 3605-3613.
8. **DeAngelis LM, Boutros D** – Leptomeningeal metastasis. *Cancer Invest*, 2005: 23: 145-154.
9. **Cheng T, O'Neill BP, Scheithauer BW, Piepgras DG** – Chronic meningitis the role of meningeal or cortical biopsy. *Neurosurgery*, 1994; 34: 590-596.
10. **Davis LE** – Tuberculous meningitis. In: Davis LE, Kennedy PGE, eds. Infectious diseases of the nervous system. Oxford: Butterworth-Heinemann, 2000: 481-498.
11. **Anderson NE, Willoughby EW** – Chronic meningitis without predisposing illness a review of 83 cases.*Q J Med*, 1987; 63: 283-295.
12. **G Froin** – Inflammations méningées avec réactions chromatique, fibrineuse et cytologique du liquide céphalo-rachidien. *Gazette des hôpitaux*, Paris, 1903, 76: 1005-1006.
13. **M Nonne** – Über das Vorkommen von starker Phase-I-Reaktion bei fehlender Lymphocytose bei 6 Fällen von Rückenmarkstumor. *Deutsche Zeitschrift für Nervenheilkunde*, 1910, 40: 161-167.
14. **Hildebrand J, Aoun M** – Chronic meningitis: still a diagnostic challenge. *J Neurol*, 2003; 250: 653-660.
15. **Demopoulos A** – Leptomeningeal metastases. *Curr Neurol Neurosci Rep*, 2004; 4: 196-204.