Large cells neuroendocrine carcinoma (LCNEC) of dural sac presented as Froin's syndrome.

L. Leonardi, L. Fionda, C. Romano, S. Morino.
Department of Neurology Mental Health and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy.

Introduzione:

Large cells neuroendocrine carcinoma (LCNEC) is a subtype of neuroendocrine cancer [1]. Froin's syndrome is characterized by marked cerebrospinal fluid (CSF) xanthochromia and hypercoagulability due to increased protein content and meningeal irritation [2, 3].

Case presentation:

Herein, we report the case of a 57-year-old caucasian man presented to ED with confusion, neck pain unresponsive to NSAID and two episodes of loss of consciousness. Head CT-scan with contrast and standard EEG were unremarkable. A contrast cerebral MRI was significant only for diffused leptomeningeal post-contrast enhancement. A CSF examination revealed xanthochromia, pleiocytosis with 79 cells/mm3, very high protein level (3,076.00 mg/dL, nv 15-45), normal glucose level. An empirical therapy with iv acyclovir and ceftriaxone was started and the patient was admitted to our neurology unit. Neurological examination at admission revealed cognitive slowing, gait instability, bilateral papilledema, without neck stiffness or focal deficits. A new lumbar puncture was performed and CSF was xanthochromic, viscous, coagulated in the tube (Figure 1, A). The protein level was severely increased (20,012 mg/dL, nv 15-45) and the cell count was 55 cells/mm3, with normal glucose level. Cytologic evaluation revealed few granulocytes and histiocitoid elements, which were characterized with immunocytofluorimetry as 40% lymphocytes (T CD3+ 80%, B CD 19 1%, NK CD 56 20%), 18% granulocytes and 42% monocytes/macrophage. Immunoelectrophoretic examination disclosed hemato-encepahlic barrier damage with Link index of 7.39 (nv 0-0.65), increased level of polyclonal IgG (11305.7 mg/L, nv <34) and albumin (4239.4 mg/L, nv <350). Bacterial (including *M. tubercolosis* and atypical Mycobacteria), fungal, parasitic, common neurothropic viruses and HIV infections were excluded with blood and CSF tests. Serum ANA, ENA profile, pANCA, cANCA dosages were within normal ranges. A total-body contrast CT-scan was unremarkable. Brain and whole spine contrast MRI showed a bulky thickness of dural sac with post-contrast enhancement, spread to spinal and encephalic leptomeninges (FIgure 1, B). A whole body ^{18}F-FDG-PET revealed a significant uptake of ^{18}F-FDG at the S2 level of the dural sac (Figure 1, C). Therefore, a CT-guided mass biopsy was performed, and three pieces of brown-red colored soft tissue (max diameter 12mm) were submitted to pathology. Microscopic examination demonstrated nodular epithelioid aggregates with small nuclear/cytoplasmic ratio, PAS-negative cytoplasm, coarse hyperchromic nuclei, and small nucleoli (Figure 1, D1-D2). Immunohistochemical staining were positive for CD56, S-100 and synaptophysine (Figure 1, D3-D4-D5) but negative for cromogranine, CK7, CK20, CDX2, TTF1 and c-kit. Ki-67 index was elevated (30-40%) (D6). These features met the histopathological diagnostic criteria for LCNEC [1]. The lack of expression of cromogranine, CK7 and CK20 is probably due to the relative indifferentiation of the tumor. A ^{68}Ga-DOTA-peptide PET-scan was positive for mild uptake of the marked peptide of the neoplasm and a therapy with iv cisplatinum plus etoposide and octreotide were started. After two weeks from admission, the patient presented severe headache, sudden vomit without nausea and bilateral sixth cranial nerve palsy with acute onset. A new head-CT scan demonstrated a tetraventricular hydrocephalus and an external ventricular shunt was placed, with improvement of neurological status. Unfortunately, the course was complicated with sepsis and the patient died four weeks later.

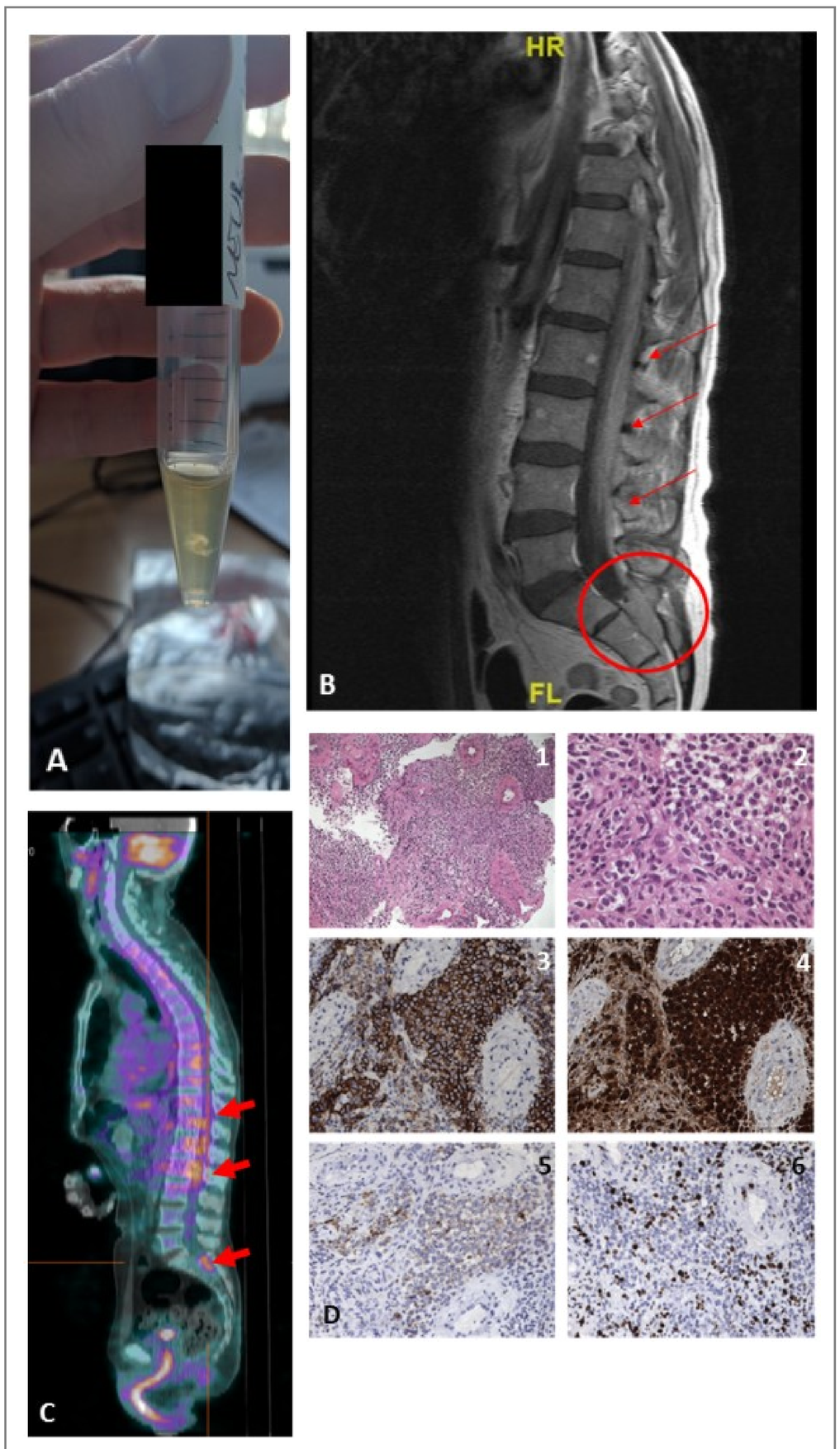

Figure 1. A. A sample of xanthochromic CSF containing a floating proteinaceous clot. B. Spinal cord MRI showing the bulky mass of the spinal cord (red circle) and the leptomeningeal post-contrast enhancing (thin arrows). C. ^{18}F-FDG-PET scan showing focal uptake at S2 level and diffuse uptake at dorsal and lumbar segments (thick arrows). D. Hematoxiylin and eosin staining 100x (D1) and 400x (D2), CD56 immunohistochemical staining 200x (D3), S-100 immuhistochemical staining 200x (D4), synaptophysin immunohistochemical staining 200x (D5), Ki-67 immunohistochemical staining 200x (D6).

Conclusioni:

LCNEC is usually a primitive lung tumor [4]. However, LCNEC originating from other sites are described in literature [5]. Tsimpas *et al.* described a single case of lung LCNEC metastasized to the dural sac, manifested with cauda syndrome [6]. In our patient, basing on whole-body PET/CT evidences, the tumor appeared to originate in the dural sac. However, the short clinical-radiological follow-up (6 weeks) does not allow excluding a silent primitive tumor of another site. Primitive paragangliomas originating from spinal canal are described in literature, and Aggarwal *et al* reported a case of primitive cauda equine paraganglioma [7]. These reports demonstrate that neuroendocrine tumors can originate in the context of spinal canal. To our knowledge, this is the first reported case of dural sac LCNEC presented as Froin's syndrome and non-resorptive hydrocephalus. We assume that the severe alterations of hemato-encephalic barrier were due to extensive leptomeningeal reactive inflammation, as corroborated by leptomeningeal post-contrast enhancing at MRI and the presence of leukocytes in CSF. Direct neoplastic infiltration of leptomeninges represents another possible mechanism. However, no neoplastic cells were found in the several CSF examinated samples.

Bibliografia

1.Gollard R, Jhatakia S, Elliott M, Kosty M. Large cell/neuroendocrine carcinoma. Lung Cancer 2010 Jul;69 (1):13-8.

2.Froin G. Inflammations méningées avec chromatique, fibrineuse et cytologique du liquide céphalo-rachidien. Gazette des hôpitaux, Paris 1903;76:1005–1006.

3.Mirza S, Adams WM, Corkhill RA. Froin's syndrome revisited, 100 years on. Pseudo-Froin's syndrome on MRI. Clin Radiol. 2008 May;63(5):600-4.

4.Schnabel PA, Junker K. Pulmonary neuroendocrine tumors in the new WHO 2015 classification: Start of breaking new grounds? 2015 May;36(3):283-92.

5.Park SB, Moon SB, Ryu YJ, Hong J, Kim YH, Chae GB, Hong S. Primary large cell neuroendocrine carcinoma in the common bile duct: first Asian case report. World J Gastroenterol. 2014 Dec 21;20(47): 18048–18052.

6.Aggarwal S, Deck JH, Kucharczyk W. Neuroendocrine Tumor (Paraganglioma) of the Cauda Equina: MR and Pathologic Findings. AJNR Am J Neuroradiol. 1993 Jul-Aug;14(4):1003-7.

7.Tsimpas A, Post NH, Moshel Y, Frempong-Boadu AK. Large cell neuroendocrine carcinoma of the lung metastatic to the cauda equine. The Spine Journal 10 (2010) e1–e5.