Neurological Sciences (2019) 40:1477–1480
https://doi.org/10.1007/s10072-019-3718-x

LETTER TO THE EDITOR

Headache, chest pain, and multiplex cranial neuropathy

Giuseppe Lauria Pinter[1,2] · Franco Ferracci[3] · Susanna Usai[1] · Daniele Cazzato[1] · Alessandra Erbetta[4] · Alessandro Perin[5] · Gianluca Marucci[6]

Received: 3 September 2018 / Accepted: 10 January 2019 / Published online: 23 January 2019

Case report

A 58-year-old man with unremarkable past medical history presented with severe episodic right-side periocular pain radiating to the frontal-temporal-parietal region, associated with unstable diplopia in the horizontal gaze. The clinical examination showed partial palsy of the right third cranial nerve sparing the intrinsic function. Prednisone 50 mg daily for 2 weeks was prescribed with sudden relief of pain and recovery of diplopia. Fifteen days after prednisone withdrawal, headache and diplopia caused by right sixth cranial nerve palsy reappeared. Intravenous methylprednisolone (1 g daily for 3 days) was given with transient full recovery. Two weeks later, the patient was readmitted due to recurrent severe headache and started prednisone 75 mg daily. Nevertheless, he developed diffuse chronic headache, bilateral sixth and partial left third cranial nerve palsy, right-side Claude-Bernand-Horner syndrome, dysphagia and dysphonia, intense chest pain, and gait unsteadiness with the need of a wheelchair. Early edema of the optic nerve was seen at the ophthalmological exam.

✉ Giuseppe Lauria Pinter
giuseppe.lauriapinter@istituto-besta.it

[1] Neuroalgology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

[2] Department of Biomedical, Clinical Sciences "Luigi Sacco", University of Milan, Milan, Italy

[3] Department of Neurology, San Martino Hospital, Belluno, Italy

[4] Neuroradiology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

[5] Oncological Neurosurgery, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

[6] Neuropathology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

Diagnostic exams

Brain magnetic resonance imaging (MRI) performed at the onset of symptoms revealed mild dural thickening overlying the apex of the petrous bone and clivus on the right side (Fig. 1). Hematological exams were negative except for a mild increase of perinuclear antineutrophil cytoplasmic (p-ANCA; 8 U/ml; normal value < 5); antibodies and positive antinucleus (1:320); and antismooth muscle (1:160) antibodies. All turned negative after the first trial of oral prednisone and remained negative over the entire follow-up period. Serum angiotensin-converting enzyme and chitotriosidase were negative. Serum immunoglobulin, IgG4, and light/heavy chain values in serum and urine were normal. Peripheral cell flow cytometry, including CD19, CD20, CD27, CD38, was negative. Urinary sediment was negative. Cerebrospinal fluid (CSF) analysis disclosed increased proteins (359 mg/dl; normal value < 45) and cells (134/mm^3 mature lymphocytes; normal value < 4) and presence of oligoclonal bands. Antibodies against neurotropic viruses (HSV 1–2 and 6–7, VZV, EBV, CMV, adenovirus, parechovirus, parvovirus), *Borrelia burgdorferi*, and mycoplasma, and screening for fungi were negative in serum and CSF. Serology for syphilis and quantiFERON (interferon-gamma release assays for *Mycobacterium tuberculosis*) were negative. Biopsies of the right temporal artery and of the nasal mucosae were negative.

Follow-up brain and spinal cord MRI at 3 months after the onset, while the clinical picture was worsening, showed meningeal thickening with intense gadolinium enhancement that extended to the midthoracic level, causing the narrowing of the spinal canal and mild cervical myelopathy (Fig. 1). Total body computed tomography (CT) scan did not show parenchymal organ lesions or vertebral bone fractures, and confirmed the diffuse meningeal thickening with intense contrast enhancement. Positron emission tomography with fluorodeoxyglucose (FDG-PET) displayed intense hypermetabolism surrounding brain and spinal cord. Brain angio-CT was negative.

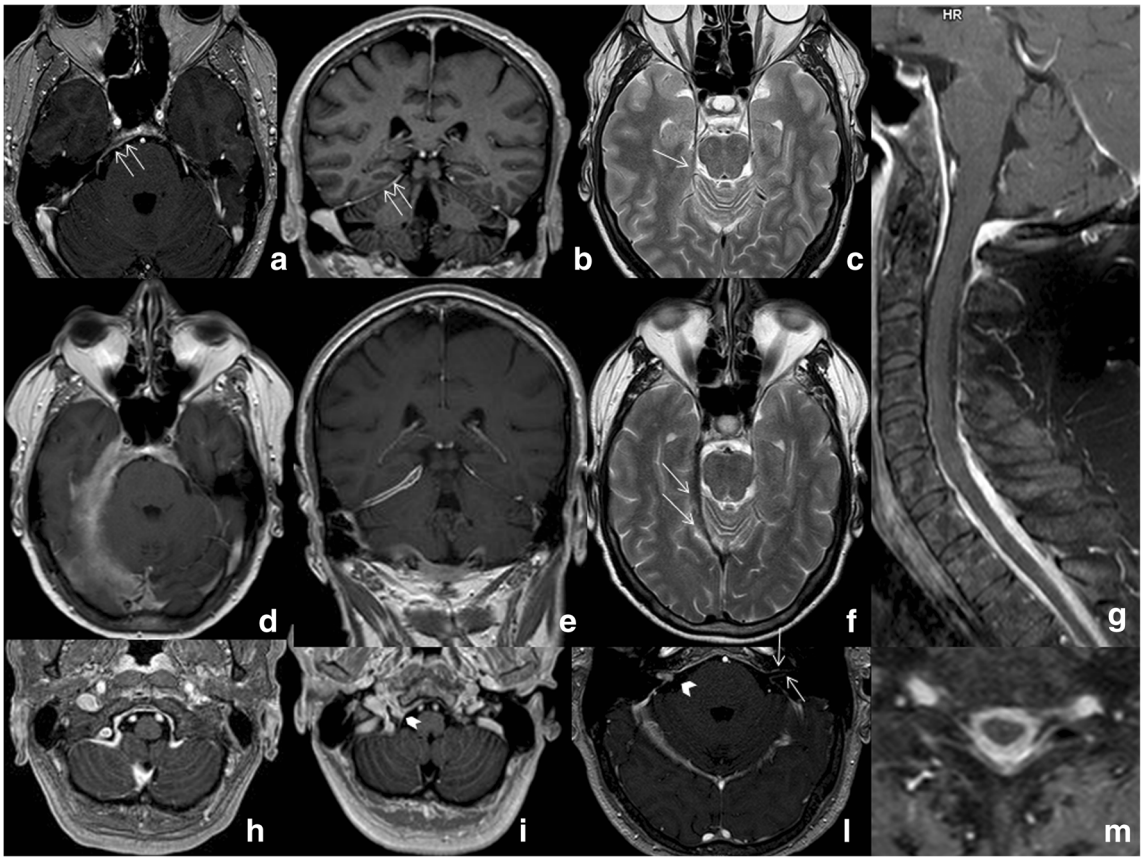

Fig. 1 Magnetic resonance imaging (MRI) at the onset of symptoms (**a**–**c**) and 3 months later (**d**–**m**). Axial and coronal T1-weighted-images (wi) with gadolinium showed mild linear dural thickening along the apex of the petrous bone, the clivus on the right side (arrows in **a**) and the right tentorium (arrows in **b**). Note also the tiny hypointensity (arrow in **c**) in axial T2 wi along the right tentorium. At 3 months, follow-up brain and spinal cord MRI findings were consistent with the clinical deterioration: axial and coronal T1 wi with gadolinium (**d**, **e**) demonstrated a marked pachymeningeal with gadolinium enhancement overlying the entire clivus and the tentorium on the right side, while the tentorial dural thickening on the right side appeared strongly hypointense in T2 wi (arrows in **f**) indicating fibrotic reaction. Pachymeningitis involved also the basicranium at the level of the medulla oblongata (**h**). Cranial nerve canals involvement was evident in axial T1 wi with gadolinium (arrows and arrows-head in **i**–**l**). The dural thickening extended throughout the cervical spine and was more marked at C7-T1 level as seen in sagittal (**g**) and axial T1 wi with fat suppression and gadolinium (**m**)

There was no nasal or oral inflammation at otolaryngology visit.

Meningeal biopsy was performed at the upper thoracic level. Histological examination revealed necrotizing, noncaseous granulomas with giant cells, histiocytes, mature lymphocytes, scattered eosinophils, and focal angiitis (Fig. 2). There was no evidence of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis which are hallmarks of IgG4-related hypertrophic pachymeningitis [1].

Treatment and outcome

Rituximab (375 mg/m^2) was administered once a week for 4 weeks. During the first month after the end of treatment, headache and chest pain intensity decreased and the patients reduced the use of steroid and analgesics. Thereafter, he showed the progressive recovery of cranial nerve functions. At 2-year follow-up, there was no clinical evidence of cranial neuropathy except for mild Claude-Bernand-Horner syndrome. The patient complained of mild chest pain but could recover all daily activities. Follow-up brain and spinal cord MRI performed at 3 and 12 months were unchanged.

Discussion

Headache associated with multiplex neuropathy of the cranial nerves is a challenging clinical picture [2] in which the diagnostic workup should be aggressive to address disease-modifying therapies. Our patient showed a life-threatening progression reflecting the impairment of cranial nerves, cervical spinal cord, and thoracic roots embedded in the meningeal thickness.

Early brain MRI and temporal artery biopsy ruled out Tolosa-Hunt syndrome and temporal arteritis [2]. Follow-up

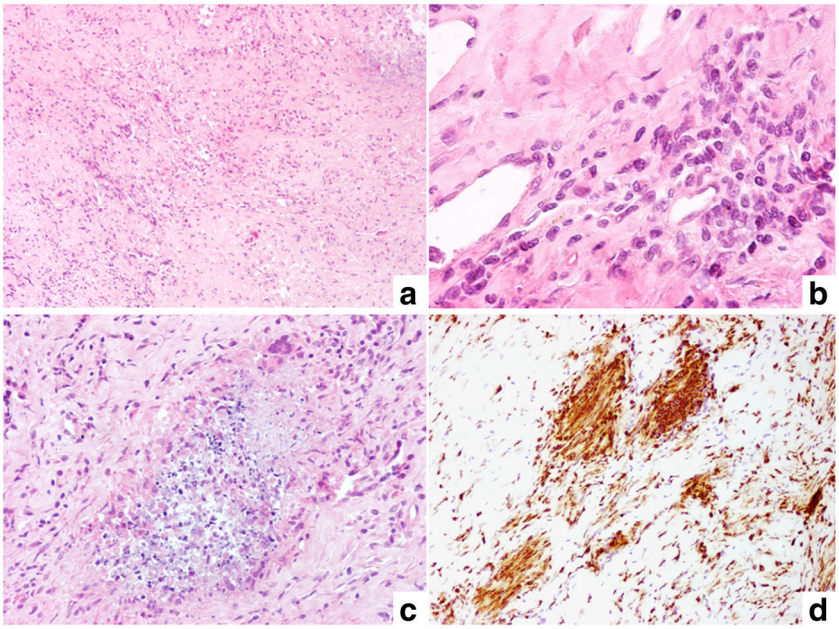

Fig. 2 Bioptic specimens presented fibrosis and extensive infiltration of giant cells, histiocytes, mature mixed B and T cell lymphocytes, and scattered eosinophils (**a**, hematoxylin and eosin, 100× magnification). Focally angiitis features were noted, with some vessels showing transmural inflammation by cytologically normal lymphocytes (**b**, hematoxylin and eosin, 400× magnification). Well-formed necrotizing granulomas were present (**c**, hematoxylin and eosin, 200× magnification) and promptly highlighted by anti-CD68 antiserum (**d**, CD68, 100× magnification)

MRI demonstrated the diffuse pachymeningitis that FDG-PET suggested to be inflammatory or infiltrative. Hematological exam, total body CT scan, and nasal mucosae biopsy findings did not support the hypotheses of IgG4-related disease [1], sarcoidosis [3], and granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis [4, 5]. This latter is diagnosed based on the following classification criteria: painful or painless oral ulcers or purulent or bloody nasal discharge (nasal or oral inflammation); pulmonary nodules, fixed pulmonary infiltrates or pulmonary cavities (abnormal chest radiograph); microscopic hematuria with or without red cell casts (abnormal urinary sediment); and biopsy of an artery or perivascular area showing granulomatous inflammation (granulomatous inflammation). The presence of two or more of these four criteria yields a diagnostic sensitivity of 88% and a specificity of 92% [6]. Our patient did not meet the diagnosis that in few cases has been described to include hypertrophic pachymeningitis among the clinical features [7, 8]. On the other hand, the presence of isolated p-ANCA has been reported in some patients with idiopathic hypertrophic pachymeningitis [9, 10].

Infectious diseases were ruled out and negative quantiFERON, along with the lack of parenchymal lesions, made tuberculosis unlikely [11]. The analysis of the CSF revealed a high level of protein that, along with the high count of mature lymphocytes, was likely associated with the severe meningeal inflammation. However, impaired CSF dynamics due to the cervical spine stenosis could have contributed to the high protein level. Meningeal biopsy was determinant to reveal the pathogenesis of the pachymeningitis and rule out lymphoma and IgG4-related forms. The unchanged meningeal thickness at follow-up MRI suggested that nerve and root impairment was likely caused by inflammatory changes rather than structural derangement that early treatment could prevent.

Hypertrophic pachimeningitis is a rare condition. Differently from what reported in recent case series [12], in our patient, rituximab treatment successfully changed the course of the diseases leading to a full recovery at 2 years. Similarly, a good response was obtained with cyclophosphamide [13] or methotrexate [14] suggesting that idiopathic hypertrophic pachimeningitis deserves aggressive immunosuppressive therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Lu LX, Della-Torre E, Stone JH, Clark SW (2014) IgG4-related hypertrophic pachymeningitis: clinical features, diagnostic criteria, and treatment. JAMA Neurol 71(6):785–793. https://doi.org/10.1001/jamaneurol.2014.243
2. Evers S (2017) Facial pain: overlapping syndromes. Cephalalgia 37(7):705–713. https://doi.org/10.1177/0333102417703761
3. Subrati N, Vaqas B, Peterson D, Patel MC (2015) Hypertrophic pachymeningitis with sarcoidosis: a rare cause of craniocervical compression. BMJ Case Rep 2015:bcr2014208604. https://doi.org/10.1136/bcr-2014-208604
4. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, Calabrese LH, Fries JF, Lie JT, Lightfoot RW Jr et al (1990)

The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 33(8): 1101–1107

5. Falk RJ, Gross WL, Guillevin L, Hoffman GS, Jayne DR, Jennette JC, Kallenberg CG, Luqmani R, Mahr AD, Matteson EL, Merkel PA, Specks U, Watts RA, American College of R, American Society of N, European League Against R (2011) Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis. Arthritis Rheum 63(4):863–864. https://doi.org/10.1002/art.30286
6. Lutalo PM, D'Cruz DP (2014) Diagnosis and classification of granulomatosis with polyangiitis (aka Wegener's granulomatosis). J Autoimmun 48-49:94–98. https://doi.org/10.1016/j.jaut.2014.01.028
7. Nagashima T, Maguchi S, Terayama Y, Horimoto M, Nemoto M, Nunomura M, Mori M, Seki T, Matsukawa S, Itoh T, Nagashima K (2000) P-ANCA-positive Wegener's granulomatosis presenting with hypertrophic pachymeningitis and multiple cranial neuropathies: case report and review of literature. Neuropathology 20(1): 23–30
8. Nakano Y, Miyawaki Y, Sada KE, Yamamura Y, Kano Y, Hayashi K, Watanabe H, Matsumoto Y, Kawabata T, Wada J (2018) Development of hypertrophic pachymeningitis in a patient with antineutrophil cytoplasmic antibody-negative eosinophilic granulomatosis with polyangiitis. J Clin Rheumatol:1. https://doi.org/10.1097/RHU.0000000000000694
9. Peng A, Yang X, Wu W, Xiao Z, Xie D, Ge S (2018) Antineutrophil cytoplasmic antibody-associated hypertrophic cranial pachymeningitis and otitis media: a review of literature. Eur Arch Otorhinolaryngol 275:2915–2923. https://doi.org/10.1007/s00405-018-5172-4
10. Zhao M, Geng T, Qiao L, Shi J, Xie J, Huang F, Lin X, Wang J, Zuo H (2014) Idiopathic hypertrophic pachymeningitis: clinical, laboratory and neuroradiologic features in China. J Clin Neurosci 21(7): 1127–1132. https://doi.org/10.1016/j.jocn.2013.09.025
11. Shobha N, Mahadevan A, Taly AB, Sinha S, Srikanth SG, Satish S, Nandagopal R, Arunodaya GR, Chandramouli BA, Shankar SK (2008) Hypertrophic cranial pachymeningitis in countries endemic for tuberculosis: diagnostic and therapeutic dilemmas. J Clin Neurosci 15(4):418–427. https://doi.org/10.1016/j.jocn.2007.03.003
12. Chen H, Zhang W, Jing J, Raza HK, Zhang Z, Zhu J, Liu Y, Cui G, Hua F, Dong L (2018) The clinical and imaging features of hypertrophic pachymeningitis: a clinical analysis on 22 patients. Neurol Sci. https://doi.org/10.1007/s10072-018-3619-4
13. Matsumoto K, Akiyama M, Kajio N, Otomo K, Suzuki K, Nishina N, Kasuya K, Oishi N, Kameyama K, Takeuchi T (2018) Adolescent PR3-ANCA-positive hypertrophic pachymeningitis: a case report and review of the literature. Medicine 97(17):e0521. https://doi.org/10.1097/MD.0000000000010521
14. Uchida H, Ogawa Y, Tominaga T (2018) Marked effectiveness of low-dose oral methotrexate for steroid-resistant idiopathic hypertrophic pachymeningitis: case report. Clin Neurol Neurosurg 168:30–33. https://doi.org/10.1016/j.clineuro.2018.02.035