Hypertrophic pachymeningitis: a case report and literature review

Abstract. The article presents a clinical analysis of a patient with undifferentiated systemic granulomatous vasculitis with predominantly pulmonary involvement and its complication of chronic hypertrophic pachymeningitis of convexity of fungal (Candida) etiology. A differential diagnosis with granulomatosis with polyangiitis has been performed. The current literature data on diagnostic criteria and treatment methods for this rare pathology are presented.

Keywords: systemic granulomatous vasculitis; hypertrophic pachymeningitis

Hypertrophic pachymeningitis (HP, G00 according to ICD-10) is a rare neurological pathology characterized by local or diffuse thickening (hypertrophy) of the dura mater and focal inflammatory changes in the brain [1, 7]. Depending on the localization of the pathological process in the brain, either basal or convexital forms of HP are distinguished. The true incidence of this pathology is unknown. It is more common in young and middle-aged males. Morphologically, HP is characterized by predominant inflammation of the meninges, resulting in diffuse or local thickening, especially of the dura mater. Typical histological features of HP include fibrosis, inflammatory infiltration of the dura mater with T-lymphocytes (CD4+) and plasma cells, and hyalinization of collagen [9].

The causes of HP are polymorphic and include at least five groups [2]:
1) prolonged intracranial hypotension (spontaneous or after the placement of shunts);
2) various infections (Lyme disease, syphilis, tuberculosis, fungal infection, cysticercosis, malignant external otitis caused by Pseudomonas);
3) systemic autoimmune diseases (Wegener’s granulomatosis, rheumatoid arthritis, sarcoidosis, Ig NMO-associated diseases, Behçet’s disease, Sjögren’s syndrome, giant cell arteritis (temporal arteritis));
4) neoplasms (dural carcinomatosis; skull metastases; central nervous system lymphoma; meningioma).
5) besides, dural hyperplasia can be idiopathic.

Rarely, a fungal infection is an etiological factor in the development of HP. In these cases, HP is more likely to occur as a result of previous respiratory infections in patients with a history of inflammation mainly in the paranasal sinuses, ear, or orbit, or as a result of prolonged immunosuppression. As the fungus grows, it penetrates the blood–brain barrier and enters the brain by local invasion, destroying the dura mater and causing inflammation, swelling, and thickening. A chronic process leads to significant thickening of the dura mater. In this case, fungal infection can cause osteomyelitis of the adjacent skull bones with the formation of soft tissue masses inside or outside the skull, rarely sepsis [4, 6].

The pathogenesis of the clinical manifestations of HP involves several mechanisms. The main one is compression, which is associated with the thickening of the dura mater, resulting in compression of the adjacent cranial nerves and cerebral vessels. A less significant mechanism of the development of HP is hypertension syndrome with impaired cerebrospinal fluid circulation and the development of internal or communicating hydrocephalus, as well as a general intoxication syndrome [3].
The clinical and neurological manifestations of HP are non-specific and associated primarily with mechanical compression of vessels and nerve structures. The most common neurological symptoms are headache, dysfunction (paresis) of cranial nerves (usually passing through the superior orbital fissure), neuro-ophthalmological disorders with visual disturbances and optic disc swelling, limb paresis, cerebellar dysfunction, simple and complex partial motor seizures, increased body temperature, etc. The diagnosis of HP is confirmed by thickening of the dura mater or detection of a soft tissue mass (e.g., cavernous sinus) on neuroimaging (CT, MRI) of the brain as well as by biopsy findings [1–9]. The treatment of HP should be comprehensive: etiotropic (antibiotic, antimycotic when indicated), pathogenetic (glucocorticosteroids), and symptomatic (analgesics, sedatives, or anticonvulsants).

We have previously published a clinical case of a patient with basal HP [3]. However, the considerable rarity of this pathology has prompted us to share our experience in the diagnosis and treatment of morphologically confirmed fungal HP of convexity.

Patient Z., 72 years old, university educated, retired (previously worked as a director of a service centre), sought medical attention at the Professor’s Advisory Medical Centre of BelMAPO in January 2020 with complaints of movement coordination disorders, speech disorders, vision disorders with body temperature over 37 °C, clumsiness in the right leg, periodic cramps in the right leg without loss of consciousness. Since childhood, he has often suffered from respiratory diseases. He has been ill since 2015 (aged 66) when low-grade fever occurred for no apparent reason. Outpatient examination: a CT scan of the lungs and mediastinum: in S3 of the upper lobe of the right lung subpleurally two large nodular masses with clear irregular rounded external contours are detected. The smaller one has an area of decay and a visible drainage bronchial lumen. On the left, there is a single small calcification in the posterior segment of the upper lobe. On the right, there is a focal shadow associated with the vascular bundle in S2. The trachea is unremarkable. The heart, large mediastinal vessels are normal. The mediastinal lymph nodes are not enlarged (Fig. 1). Conclusion: a CT pattern of infiltrative and destructive process in both lungs. Therefore, he was referred to Minsk City Clinical Oncologic Dispensary for hospitalization. A lung tissue biopsy was performed there. The results of histological examination: pulmonary tissue fragments with the presence of gross fibrosis with foci of necrosis, in other parts of the lung tissue — nonspecific low-grade inflammation with microabsorption. Based on the findings, a diagnosis of meningoencephalitis of unspecified etiology (differentiate with systemic vasculitis) is made. Deep mycosis of the lungs? Condition after surgical treatment (the S3 resection on the right).

He was referred to the Department of Rheumatology for further treatment, where he was treated with glucocorticosteroids and showed positive changes. The patient was diagnosed with granulomatosis with polyangiitis (previously referred to as Wegener’s granulomatosis in the literature) with CNS and lung involvement (later the patient received treatment on an outpatient basis). Subacute secondary meningoencephalitis. Right-sided hemianopsia, moderate coordination disorder. Complicated optic disc swelling late stage.

He was followed up by a rheumatologist in 2016–2017 and received monthly intravenous cyclophospham. However, his condition deteriorated intermittently, and pulse methylprednisolone therapy was prescribed, after which...
his condition improved. In 2017, another brain MRI scan revealed the evidence of transverse and sigmoid sinus thrombosis, which was not clinically evident. Since 2018, he has been continuously taking medrol (8–16 mg/day) and azathioprine. The patient’s condition was compensated and stable. In January 2020, for the first time, seizures in the right leg without loss of consciousness and clumsiness in the right leg occurred and he first was consulted by a neurologist as an outpatient at the Professor’s Advisory Medical Centre of BelMAPO.

During the examination, the condition was satisfactory, with normal nutrition. Blood pressure — 120/80 mmHg, heart rate — 72 bpm, a pulse is rhythmic. Somatic status: compensated. Neurological status: conscious, contactable. No apparent cognitive impairment. Pupils D = S, response to light is preserved. No nystagmus or oculomotor disturbances. The tongue is along the midline. The soft palate is mobile in phonation. The strength in the extremities is adequate. Deep reflexes from the arms and legs are high, D = S. The tone in the extremities is unchanged. A positive Babinski sign. No meningeal signs. He moves independently, with mild ataxia while walking. He is stable during the Romberg test. The function of the pelvic organs is not impaired. The results of the previous tests have been analyzed: complete blood count: leukocytes — 13.30 • 10⁹, hemoglobin — 137 g/L, erythrocytes — 4.62 • 10¹², platelets — 341 • 10⁹, eosinophils — 1 %, neutrophils — 72 %, lymphocytes — 18 %, monocytes — 9 %, ESR — 25 mm/h. Blood chemistry test: total protein — 65 g/L, urea — 5.7 mmol/L, creatinine — 99 mmol/L, total cholesterol — 5.1 mmol/L, bilirubin — 8.3 mmol/L, glucose — 4.71 mmol/L, ALT — 16.4 U/L, AST — 26.1 U/L, sodium — 147 mmol/L, potassium — 5.3 mmol/L, chlorine — 112 mmol/L. Urinalysis: straw-yellow, transparent, acidic, specific gravity — 1012, leukocytes — 5–7 per field of view. ECG: sinus rhythm, horizontal QRS axis of the heart. Sputum and CSF examination microscopically and by GeneXpert: no Mycobacterium tuberculosis DNA detected. Blood, CSF for sterility (repeated): no growth in culture. CSF (2017): protein — 0.58 g/L, glucose — 3.1 mmol/L, cytosis — 26.7 • 10⁶ (lymphocytes — 43 %, neutrophils — 34 %, macrophages — 4 %). Markers of antiphospholipid syndrome (2017): IgM cardiolipin — 1.2 GPL, IgG cardiolipin — 2.5 GPL; no IgM β₂-glycoprotein; IgG β₂-glycoprotein — 6.3 U/ml (normal). Autoimmune disease markers (2015): antinuclear antibodies titer < 31 (normal titer < 40), cytoplasmic anti-neutrophil antibodies titer 32.2 (normal titer < 20). Thyroid ultrasound (2015): left lobe — 10 × 11 × 35 mm, right lobe — 11 × 11 × 34 mm; the echotexture is heterogeneous. Abdominal ultrasound (2015): a cyst in the right kidney, hepatic hemangioma. Cardiac ultrasound (2015): a dilated ascending aorta, atherosclerosis of the aorta and aortic valve cusps, atherosclerotic changes in the coronary arteries, moderate cardiocclerosis. Cardiac contractility is satisfactory. Ejection fraction — 73 %. EEG (2020): moderate diffuse dysrhythmic changes. No clear paroxysmal pathological activity was detected. Brain MRI (2020): negative changes in the form of a moderate increase in the size of previously detected areas of hyperintense T2W and FLAIR signal, mass effect in the parietal and occipital lobes of both hemispheres, thickening of the dura mater on
convexity. Following intravenous contrasting, a more pronounced (compared to the previous tests) heterogeneous accumulation of the contrast agent in the posterior parietal and occipital lobes persists (Fig. 3A–D).

Ophthalmologist (2016): right-sided hemianopsia, the ocular fundus: OU, the optic discs are hyperemic, the borders are blurred, the arteries are narrowed, the veins are dilated. Conclusion: complicated optic disc swelling with right-sided hemianopsia, the contours are clear, the arteries are sclerosed, the veins are of irregular caliber, tortuous. Otorhinolaryngologist (2017): chronic bilateral maxillary sinusitis, without bleeding and necrotic changes of the nasal mucosa.

To clarify the nature of the process in the meninges, the patient underwent a biopsy of the dura mater in the Department of Neurosurgery in March 2020. Conclusion: the fragments of small vascular fibrous tissue with multiple granulomatous inflammations embedded in hyalinosis with accumulations of leukocytes and bacilliform and rounded microorganisms (like Candida fungi and their spores, Fig. 4) in the centre. Eosinophils are present in the inflammatory infiltrate. The morphological pattern favours a fungal lesion.

We diagnosed undifferentiated systemic granulomatous vasculitis with predominant pulmonary involvement. Complications: chronic hypertrophic pachymeningitis of convexity of fungal (Candida) etiology. Pyramidal insufficiency on the right, hypertensive syndrome, partial hemianopsia on the right, rare partial motor seizures.

He was consulted by an infectious disease doctor and received the recommendations as follows: reduction of the dose of medrol, a long-term course of antimycotic therapy. The patient was prescribed medrol in a dose of 8 mg per day. During the follow-up for 1.5 years: the coordination of movements improved, clumsiness in the right leg does not bother him, but periodic right leg seizures without loss of consciousness are recurring.

Thus, a patient with a history of frequent respiratory diseases developed a subacute clinical picture of systemic granulomatous vasculitis with predominantly

Figure 3. Brain MRI of the same patient (2020): negative changes in the form of a moderate increase in the size of previously detected areas of hyperintense T2W and FLAIR signal, mass effect in the parietal and occipital lobes of both hemispheres (A, B, C), thickening of the dura mater on convexity (C, D)
The clinical and laboratory findings and the course and changes of the patient’s disease made it possible to exclude a group of neoplastic processes, intracranial hypotension and bacterial infection as the etiology of HP. One of the autoimmune connective tissue diseases was suspected in the early stages of the disease. Among various clinical forms of systemic vasculitis, the differential diagnosis with granulomatosis with polyangiitis (Wegener’s granulomatosis), a diagnosis that the patient had previously had and with which he had been followed for over five years, was the most difficult to make. This pathology (synonymous with rhinogenic angioedema) is characterized by a triad of organ involvement of the upper respiratory tract, lungs, and kidneys. In the vast majority of patients (up to 100 % of cases), necrotizing granulomatous inflammation of the upper respiratory tract progresses (ulcerative necrotizing rhinitis, nosebleed from eroded vessels, mucosal atrophy, involvement of the trachea and larynx with subclavian granuloma formation, nasal cartilage erosion). Pulmonary involvement (50–70 cases) is characterized by necrotizing granulomatous inflammation, which is identified radiographically as nodules or infiltrates prone to disintegration and cavity formation. Renal involvement occurs in 80 % of patients, often in the form of glomerulonephritis with the rapid progress of renal failure. Other organs and systems are involved much less frequently, and CNS involvement is not considered a characteristic feature of the disease [10]. A high serum C-ANCA titer and biopsy results confirming granulomatous inflammation of the involved tissue are of diagnostic value. Our patient did not have common clinical symptoms of ENT organ and kidney involvement. Common symptoms: in this case, a positive anti-neutrophil cytoplasmic antibody test and lung biopsy results were common for ANCA-associated vasculitis and are not specific for granulomatosis with polyangiitis. The clinical, laboratory, and biopsy findings in our patient did not match any of the known clinical forms of granulomatous (necrotizing) vasculitis. For this reason, the primary diagnosis was undifferentiated systemic granulomatous vasculitis with predominantly pulmonary involvement.

This case is of great interest due to the difficulty of diagnosis and the development of a complication of chronic recurrent hypertrophic pachymeningitis of convexity of fungal (Candida) etiology.

References

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Гіпертрофічний пахіменінгіт: клінічний випадок і огляд літератури

Резюме. У статті наведений клінічний розбір пацієнта з недиференційованим гранулематозним системним васкулітом із переважним ураженням легень і його ускладненням у вигляді хронічного гіпертрофічного конвекситального пахіменінгіту грибкової (Candida) етіології. Проведена диференційна діагностика з гранулематозним поліангіїтом. Наведені сучасні літературні дані з критеріїв діагностики й методів лікування цієї рідкої патології.

Ключові слова: системний гранулематозний васкуліт; гіпертрофічний пахіменінгіт