Case report

Autoimmune meningitis and encephalitis in adult-onset still disease – Case report

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Introduction: Adult-onset Still disease (AOSD) is a rare systemic inflammatory disease of unknown cause. Its symptoms usually include persistent fever, fugitive salmon-colored rash, arthritis, sore throat (not specific), but it may also lead to internal organs’ involvement, which presents with enlargement of the liver and spleen, swollen lymph nodes, carditis or pleuritis – potentially life-threatening complications. In rare cases, AOSD can cause aseptic meningitis or encephalitis.

Case presentation: We report a case of 31-year-old male patient, who was referred to neurological department for extending diagnostics of frontal lobes lesions with involvement of adjacent meninges. Abnormalities have been revealed in brain MRI, which was performed due to persistent headaches, visual disturbances, fever, fatigue and cognitive decline. Wide differential diagnosis was performed including laboratory findings, contrast enhanced MRI, MR spectroscopy, flow cytometry and finally brain biopsy to exclude neoplastic or infectious origin. Final diagnosis of autoimmune meningoencephalitis in adult-onset Still disease has been made.

Conclusion: Adult-onset Still disease is a rare cause of inflammatory changes in central nervous system, which if diagnosed, may be treated successfully with steroids (commonly available agent), intravenous immunoglobulins or more specific immunomodulating regiments.

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1. Introduction

Meningoencephalitis is a condition that simultaneously involves both meninges and brain parenchyma [1]. Clinical manifestation and severity depend on several factors, such as etiology, lesion’s location (diffuse vs focal), potential complications etc. Prodrome symptoms usually include fever, headache, nausea and vomiting, lethargy, fatigue, and usually they can be followed by altered mental status, behavioral and personality changes, hypersomnolence, language difficulties, focal neurological deficits (e.g., hemiparesis, cranial nerves palsies). If not treated, may lead to seizures, increased intracranial pressure, coma and death. Patient’s history may
give clues concerning etiology (e.g., mosquito tick bites, certain animal bites, comorbidities including coexisting systemic autoimmune disorder, exposure to certain chemical, toxic or intoxicating substances or drugs etc.). Physical examination is also of great importance (e.g., rash, lymphadenopathy, hepatosplenomegaly, herpetic skin lesions) [2].

Differential diagnosis is complex especially if there is no history of preceding protozoans, viral or bacterial infection or travel health problems. But even the obvious infectious etiology requires infectious agent identification with meticulous serological testing, lesions smear, blood or CSF cultures [2].

Autoimmune encephalitis is a complex disease related to diverse immunologic response to coexisting neoplastic or non-neoplastic condition, or resulting from central nervous system vasculitis (primary or secondary). Autoimmune encephalitis can be suspected if there is evidence of serologic autoimmunity and intrathecal inflammation in the cerebrospinal fluid sometimes combined with diffused brain lesions [3].

As autoimmune causes of encephalitis are less common, diagnosis is usually made by an exclusion of other, more probable causative factors (infectious, toxic, metabolic, vascular or structural damage). Therefore, while diagnosing a patient with symptoms suggestive of meningoencephalitis several laboratory, neuroimaging and serological investigations must be carried out. Apart from typical laboratory evaluation (including complete blood counts, erythrocyte sedimentation rate, C-reactive protein, renal, liver and thyroid function, vitamin B complex deficiency), the markers of underlying systemic autoimmune disease should be obtained (e.g. anti-nuclear antibodies [ANA], anti-neutrophil cytoplasmic antibodies [ANCA], lupus anticoagulant [LA]). Cerebrospinal fluid analysis is crucial for exclusion of infectious and neoplastic background, moreover it can provide an evidence of intrathecal inflammation [4–6]. Magnetic resonance imaging is the method of choice for identification of vascular, demyelinating or neoplastic lesion. Due to increasing number of patient with antibodies-specific encephalopathies, the presence of some autoantibodies should be assessed (e.g. anti-NMDA receptor, anti-CASPR2 or anti-LGI1) [3–6].

Autoimmune encephalitis can produce a wide range of symptoms, that may mimic other neurological or psychiatric disorders, (e.g. limb or cranial nerve palsies, ataxia, involuntary movements, cognitive impairment, agitation, hallucinations or delirium, severe anxiety). Immunomodulating therapy may give improvement and it may include steroids, plasmapheresis or intravenous immunoglobulin (IVIG) [5,6]. Removal of triggering factor (if present, such as coexisting neoplasm) is also effective [5,6]. In case of known cause that triggers immune response guided treatment methods may be required [5,6].

2. Case report

31-Year-old male patient was admitted to the neurological department due to frontal lobes lesions involving meninges of unknown etiology. Abnormalities have been revealed in brain MRI, which was performed due to persistent headaches, visual disturbance, fever, sleepiness, cognitive decline and weight loss. Previously the patient was hospitalized in other neurological ward and infectious disease department, where tuberculosis and bacterial meningitis have been excluded. As a 6-month-old baby the patient was diagnosed with phenylketonuria. He also reported that he had been treated for a long time because of Still disease diagnosis, but he stopped this treatment because long remission.

At admission the neurological examination was normal, apart for slowness of movements and apathy.

Contrast-enhanced MRI showed bilateral frontal lobes abnormalities, including poorly margined cortical and subcortical hyperintensities on T2 weighted and FLAIR images with lobes swelling, little mass effect and absence of parenchymal enhancement (Fig. 1a and b). Abnormal meningeal thickening and enhancement especially prominent in both frontal regions including anterior part of falx cerebri was detected on gadolinium-enhanced T1-weighted image (Fig. 1c and d). Brain MRI was assessed by a neuroradiologist as non-specific localized hypertrophic pachymeningitis with frontal brain edema. Lesions location was not typical for tuberculosis.

Basic laboratory findings (such as complete blood counts, liver and renal testing, electrolytes, coagulation, CRP, serum protein electrophoresis) were normal apart from increased sedimentation rate (16 mm/h). HBV, HCV and HIV1/HIV2 antibodies were negative. Lupus antigen was present, unlike anticytodioplin (aCL) antibodies, which were absent. Serum rheumatoid factor and anti-nuclear antibodies were not performed as they were negative in several previous measurements. Ferritin was normal (75.1 ng/ml with normal range of 22–322 ng/ml). The serum level of glycosylated ferritin was not measured as the test was not available in author’s research center.

Lumbar puncture was performed. General CSF analysis exhibited normal results except for slightly increased number of white cells (6 cells in mm³ with normal range of 0–5 cells in mm³, 82% of lymphocytes). The cerebrospinal fluid immunoglobulin index revealed several abnormalities: IgG CSF 6.70 mg/dl (normal range: 0.63–3.35), IgG CSF/protein CSF 19.1% (normal range: 0.0–12.0), IgG Index 1.11 (normal range: 0.00–0.70), IgG daily synthesis 3.11 mg/24 h (normal range: 0.00–3.30) and local IgG synthesis 2.78 mg/dl (normal range: <0.01). Oligoclonal bands were also present. CSF cytologic examination did not reveal any abnormal (neoplastic) cells.

Both serum and CSF testing for HSV DNA were negative. Serum Toxoplasma gondii antibodies were positive (which is probably an accidental finding as seroprevalence of Toxoplasma gondii antibodies in a healthy population is 20–24%) [7,8]. CSF Toxoplasma gondii antibodies were negative (0 IU/ml with normal range of <4 IU/ml). Serum and CSF ACE levels were normal.

The patient’s case was consulted with infectious disease specialist, who advised anti-viral therapy – acyclovir was administered intravenously, but clinical improvement was not achieved.

To help identify a nature of brain lesions MR spectroscopy was performed (not shown). The conclusion suggested active neoplastic or inflammatory process with decrease NAA/Cr ratio and increased Cho/Cr ratio.

During second hospitalization – a month later, contrast enhanced MRI revealed further progression of frontal lesions.
with thickening of the cerebral falx and the meninges covering frontal lobes. Flow cytometry excluded the presence of lymphoma cells in cerebro-spinal fluid. The patient was then transferred to the Department of Neurosurgery and underwent brain biopsy. The histopathological analysis of biopsy material revealed thicken proliferating dura mater with diffuse desmoplasia (Fig. 2a), inflammatory infiltration and granular vasculitis (Fig. 2b).

During a visit in out-patient clinic a month later the patient revealed that he had been treated due to adult-onset Still disease for nearly 5 years and the treatment was completed 4 months before neurologic symptoms onset. The diagnosis was made 6 years earlier when the patient suffered from arthralgia, high fevers, salmon-colored rash over lower extremities, abdominal lymphadenopathy and splenomegaly. Leukocytosis with granulocyte predominance was also present. The

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**Fig. 1** – Baseline neuroimaging of patient with adult-onset Still’s disease. (a and b) Axial FLAIR images showing diffuse bilateral frontal hyperintensities with swelling and little mass effect. (c and d) Axial gadolinium enhanced T1 weighted images demonstrate relatively thick pachymeningeal enhancement of the anterior cranial fossa and in the dural reflections of the anterior falx with a hypointense frontal edema.

**Fig. 2** – Stereotactic biopsy specimen, hematoxylin-eosin staining. (a) The growth of fibrous or connective tissue (desmoplasia), (b) mononuclear cells inflammatory infiltration and granular vasculitis.
patient received intravenous steroids as first-line therapy followed by oral steroids. Due to poor symptoms control methotrexate was added with good outcome (clinical and laboratory remission was achieved).

Taking all the above into consideration, after exclusion of infectious, other systemic and neoplastic cause, the suspicion of autoimmune meningitis and encephalitis in adult-onset Still’s disease was raised and immunosuppressive treatment had been started. Methylprednisone i.v. was introduced as the first-line therapy and followed by oral prednisone. Contrast brain MRI performed a month later, showed significant remission of inflammatory lesion within brain tissue and meninges (Fig. 3). The patient has been referred to rheumatology ward, where autoimmune vasculitis has been suspected.

Currently, the patient is treated with subcutaneous methotrexate 25 mg/week, and oral prednisone 35 mg daily. He reports further regression of his symptoms.

3. Discussion

Still’s disease was first described in children in 1897 by George Frederic Still, an English physician [9]. Cases of adults with similar clinical presentation were later described by Eric Bywaters in 1971 [10]. Adult onset Still’s disease is a rare condition with an estimated prevalence of 1 person per 100,000 people, what make its potential neurological complications even rarer [11]. The diagnosis of adult-onset Still’s disease is made via exclusion, when typical symptoms are present and other potential causes are absent. Preliminary criteria for classification of adult Still’s disease were proposed by Yamaguchi et al. in 1992 (Table 3) [12].

These criteria were modified in 2001 by Fautrel et al., who emphasized the value of ferritin and glycosylated ferritin level in diagnosing adult onset Still’s disease (Table 2) [13]. Presented patient fulfilled both Yamaguchi and Fautrel criteria when he was diagnosed with AOSD [12,13].

Systemic involvement is frequent and it includes potentially life-threatening conditions, such as pericarditis, endocarditis or/and myocarditis, pericardial tamponade, pleuritis, pneumonitis, acute respiratory distress syndrome (ARDS), alveolar hemorrhage, multiorgan failure, fulminant liver failure, disseminated intravascular coagulation (DIC syndrome), thrombotic microangiopathy, glomerulopathy [14]. Neurological complications are rare and occur in 7–12% of patients with adult onset Still’s disease [15,16]. In the course of disease several neurological syndromes have been reported, such as cranial nerve palsies, seizures, aseptic meningoencephalitis, posterior reversible encephalopathy syndrome, Miller-Fisher syndrome, and peripheral neuropathy [17–21].

![Fig. 3 – Follow-up neuroimaging. FLAIR (a and b), and contrast enhanced T1-weighted sequences (c and d) revealed reduced volume of the frontal lobes lesions, resolution of the frontal edema and the mass effect, overall enhanced T1-weighted signal and dural thickening is decreased compared with the baseline image.](image-url)
There is a number of systemic autoimmune disorders affecting brain (e.g. systemic lupus erythematosus, Susac’s syndrome, Whipple’s disease, Sjögren’s syndrome, Behçet’s disease). A link between immune dysfunction and brain involvement is complex and may include cerebral vascular changes or presence of antibodies targeting synaptic proteins [22]. Our patient fulfilled AOSD diagnostic criteria and for many years had been treated successfully with immunosuppressive agents. Laboratory remission has been achieved, which explains normal serum laboratory results. CSF exam in the patient showed only small pleocytosis. We did not observed neutrophilic predominance, which was described in other case reports considering aseptic meningitis in adult onset Still’s disease [23,24].

Interestingly, lupus anticoagulant (LA) was found – the positive result for LA does not have to put in question Still’s disease diagnosis. Lupus anticoagulant (LA) is a heterogeneous group of antibodies, which is usually present in patients with systemic lupus erythematosus, however at least 50% of people with lupus anticoagulants do not present with this condition [25]. Moreover the prevalence of LA in the general population is about 10% [26]. It may be also present in other connective tissue disorders, malignancies and infections or may be drug-induced [27]. Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus were also not met, neither during current hospitalization nor retrospectively [28].

Establishment of the diagnosis of Still’s disease needs careful exclusion of other possible etiology of aseptic meningoencephalitis. In our patient CNS infectious diseases have been excluded, including tuberculosis, Borrelia burgdorferi, syphilis, CNS fungal infection, neurocysticercosis, HSV infection. Other immune disorders have been also considered (e.g. Wegener granulomatosis, rheumatoid arthritis, sarcoidosis, Sjögren disease, giant cell arteritis) with negative results. Tumor (including lymphoma) or metastases were excluded. Brain biopsy confirmed the presence of chronic inflammatory process within brain tissue and meninges.

Data on neuropathological findings in adult onset Still’s disease is scarce. In single case reports of adult-onset Still’s disease with central nervous system involvement (CNS) brain pathological examination showed demyelinating lesions [29,30]. In other case report brain biopsy revealed reactive inflammatory injury with extensive Alzheimer type 2 cells and microvascular changes [31]. In several other reports multisystem involvement, including CNS, was reported as a result of macrophage activation syndrome due to uncontrolled proliferation of T lymphocytes and well-differentiated macrophages [32,33]. Presented patient met the Criteria for autoantibody negative but probable autoimmune encephalitis proposed by Graus et al. [34]: the progression of symptoms was rapid and had begun shortly after discontinuation of immunosuppressive treatment, well defined syndromes of autoimmune encephalitis were excluded, patient had MRI abnormalities, small CSF pleocytosis and positive brain biopsy showing inflammatory infiltrates, the other reasonable alternative causes were excluded.

All the above, together with good response to steroids made Still’s disease a probable cause of brain lesions detected in brain MRI in our patient.

The neurological complications of Still disease are extremely rare, so there is no established treatment recommendations, although methotrexate and steroids are preferably used drugs.

### 4. Conclusion

Adult onset Still’s disease is a rare systemic inflammatory disease of unknown cause with well-defined systemic symptoms and potentially life-threatening complications. Central nervous system is rarely affected by inflammatory process in Still’s disease. Nevertheless in case of neurological deficits appearance and brain MRI abnormalities in patient with Still’s disease underlying autoimmunological process should be considered.

### Conflict of interest

None declared.

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The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES