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Short Communication

Neuromyelitis optica, atypical hemophagocytic lymphohistiocytosis and heterozygous perforin A91V mutation

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ABSTRACT

Neuromyelitis optica is an autoimmune demyelinating inflammatory disease characterized by optic neuritis and myelitis with anti-aquaporin 4 antibodies. Hemophagocytic lymphohistiocytosis is a severe systemic inflammatory syndrome that can present in a genetic primary form or secondarily to infective, neoplastic or autoimmune diseases. Our case discusses the first reported case of atypical late-onset hemophagocytic lymphohistiocytosis in a patient with neuromyelitis optica, with multiple triggering factors and carrying the common A91V hypomorphic perforin mutation, that blurs the distinction between primary and secondary forms.

1. Introduction

Neuromyelitis optica (NMO) is an immune-mediated demyelinating inflammatory disease characterized by optic neuritis (ON), longitudinally extensive transverse myelitis (LETM) and positive anti-aquaporin 4 antibodies (anti-AQP4). Other symptoms due to involvement of organs and structures have been reported, defining a widening clinical syndrome called anti-AQP4 autoimmunity syndrome or NMO spectrum disorder (NMOSD) (Weinshenker and Wingerchuk 2017).

Hemophagocytic lymphohistiocytosis (HLH) is a severe systemic inflammatory syndrome caused by defect in NK-cell cytotoxicity leading to an unchecked activation of the immune system. The typical presentation is characterized by fever, splenomegaly, cytopenias, hyperferritinemia, elevated triglycerides, hypofibrinogemia and elevated serum soluble CD25. Neurological involvement is common and very variable. Familial early-onset HLH (FHL) are caused by genetic mutations in PRF1, UNC13D, STX11, STXBP2 or associated to Griscelli syndrome type 2, Chediak-Higashi syndrome, Hermasky-Pudlak syndrome or X-linked lymphoproliferative syndromes. Atypical late-onset forms have been also described. Secondary HLH can be triggered by infections, malignancies, autoimmune, drugs or metabolic diseases. Hematological malignancies are commonly associate with secondary HLH. In the context of autoimmune disease like systemic lupus erythematosus, Still's disease or anti-phospholipid syndrome, HLH is sometimes called macrophage activation syndrome (MAS). Numerous infections can trigger HLH, viral, bacterial and fungal. Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) are the two most common infection associated, and can sometime represent the trigger for the presentation of a familial form (Janka and Lehmberg 2014).

We present here an adult patient with NMOSD treated with azathioprine (AZA). He developed atypical HLH during a CMV reactivation. Despite normal NK numbers, functionality revealed low perforin expression. Thus, perforin gene PRF1 was studied with the finding of the common hypomorphic polymorphism c.272C > T (p.Ala91Val or A91V).

2. Case report

We report the case of a 48 years old man with LETM with involvement of the nerve roots. Patient history was unremarkable except for a ventriculoperitoneal shunting more than twenty years before because of hydrocephalus.

On January 2014 he presented with bilateral lower limbs asthenia and dysesthesias on the trunk. The patient was treated as a Guillain-Barré syndrome with high dose IVIg, even though clinical and electrophysiological presentation was already suggestive of a radicular involvement.

In March due to worsening of the symptoms, a spine MR revealed a diffused enlargement of the spinal cord from C6 to D9 with a central medullary altered T2 signal and an hyper-intensity at the D3-D4 level

Abbreviations: HLH, Hemophagocytic lymphohistiocytosis; NMO, Neuromyelitis optica; NMOSD, Neuromyelitis optica spectrum disorder; LETM, Longitudinally extensive transverse myelitis; Anti-AQP4, Anti-Aquaporin 4 antibodies; AZA, Azathioprine; CMV, Cytomegalovirus

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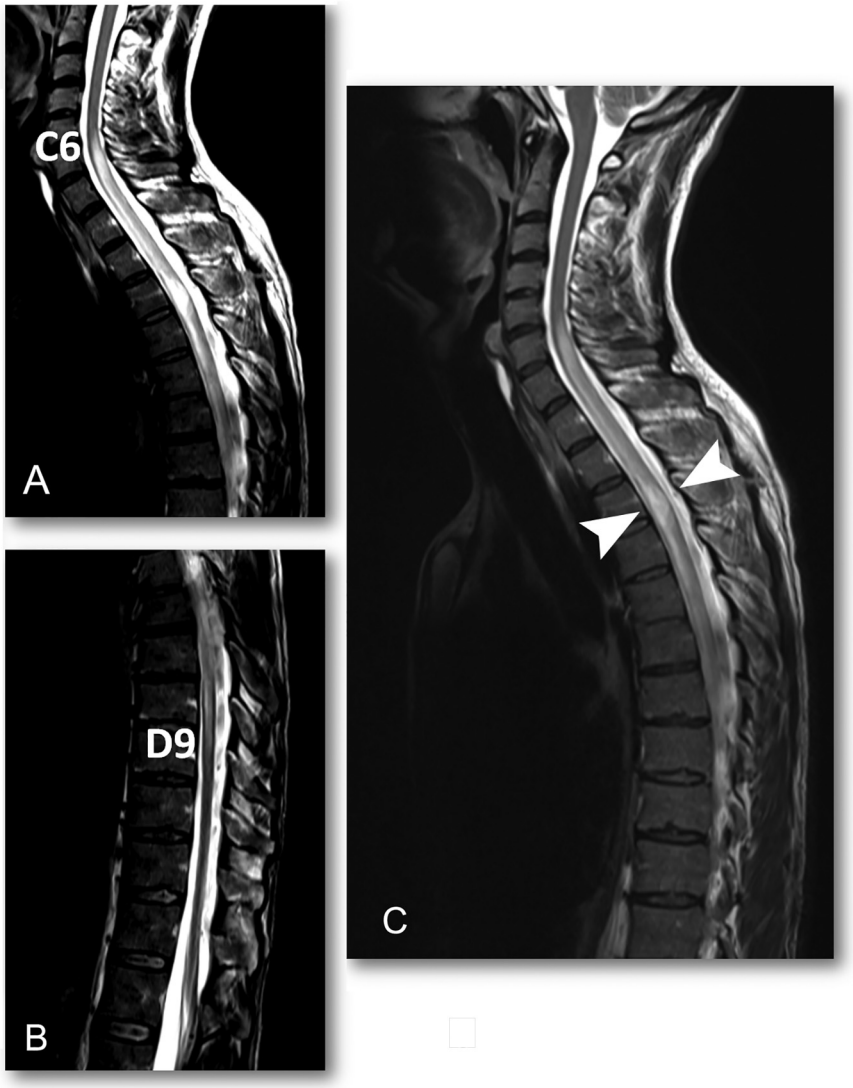

Fig. 1. Spine MR showing diffused enlargement of the spinal cord from C6 (A) to D9 (B) with a central medullary altered T2 signal and an hyperintensity at the D3-D4 level (C).

[Fig. 1]. The patient was treated with corticosteroids with good response.

In August he experienced a relapse of myelitis. In this occasion anti-AQP4 antibodies were demonstrated, the diagnosis of NMO was made and azathioprine was started.

After six months follow-up he developed recurrent fever, associated with splenomegaly and lymphadenopathies. Blood exams showed pancytopenia and elevation of serum ferritin. In spite of an overt inflammatory state, levels of fibrinogen were halved compared to previous controls, even though still above the reference range. There was also a moderate elevation of liver enzymes, gamma-GT and LDH. CMV reactivation was demonstrated by PCR (> 15,000 viral copies/mL). Triglycerides values were normal. Since the patient was already fulfilling 4/8 HLH 2004 criteria(Henter et al. 2007) (fever, splenomegaly, cytopenia, ferritin) plus a relevant reduction of fibrinogen, a presumptive diagnosis of virus-associated HLH was formulated and the patient was treated with corticosteroids, ganciclovir and IVIg [Table 1].

Further testing for NK-cell activity assessed by flow cytometry for perforin and CD107a displayed a reduction of perforin expression suggesting an hypomorphic perforin mutation [Fig. 2]. Further testing for NK-cell activity assessed by flow cytometry perforin expression, which was reduced [Fig. 2], and degranulation by CD107a expression which was normal (data not shown) (Shabrish et al. 2016; Weren et al. 2004). The expression of perforin was similar both during HLH and after complete remission as well as after RT and 40 °C incubation (Supplementary Materials). These data suggested a hypomorphic perforin mutation.

Genetic sequencing of PRF1 confirmed the presence of the heterozygous hypomorphic polymorphism A91V. Azathioprine was suspended and after the resolution of the HLH, due to rising titers of anti-AQP4

Table 1
Blood test exams before and during the HLH, and reference ranges.

	Patient values		Ref
	before HLH	during HLH	
Hb	12.5	8.6	12–16 g/dL
WBC	6.02	3.6	4–10 × 10^9/L
Neutrophil	2.85 (47.3%)	2.46 (68.5%)	1.5–7.5 × 10^9/L
Lymphocyte	2.30 (38.2%)	0.62 (17.2%)	0.5–5.0 × 10^9/L
Platelet	215	76	140–440 × 10^9/L
Ferritin	326	726	8–252 ng/mL
Triglyceride	226	155	< 150 mg/dL
GOT	23	92	15–37 U/L
GPT	51	166	30–65 U/L
LDH	232	286	84–246 U/L
γGT	31	63	5–85 U/L
Fibrinogen	424	203	200–450 mg/dL