Clinically reversible ustekinumab-induced encephalopathy: case report and review of the literature

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***Abstract*:** Ustekinumab, a monoclonal antibody against interleukin (IL)-12 and IL-23 approved for the treatment of Crohn's disease, has shown to be an effective therapy with a favourable safety profile. Clinical trials and real-world studies have reported very few neurological adverse events, including posterior reversible encephalopathy syndrome, idiopathic intracranial hypertension and headache. We describe the case of a 48-year-old man with Crohn's disease who initiated treatment with ustekinumab on top of ongoing treatment with methotrexate 25 mg/week who presented with an acute-onset encephalopathy that rapidly evolved to severe tetraparesis and akinetic mutism, associated with extensive leukoencephalopathy and restricted diffusion on brain magnetic resonance imaging (MRI), 1 month after the second dose of ustekinumab. Comprehensive in-patient diagnostic testing ruled out vascular, demyelinating, metabolic, tumoral and infectious etiologies. Brain biopsy showed patchy infiltrates of foamy histiocytes with perivascular distribution, associated with edema, diffuse astrocytic gliosis and focal perivascular axonal destruction without demyelination, and ustekinumab-induced neurotoxicity was suspected. After drug discontinuation, the patient presented a complete clinical recovery despite the persistence of leukoencephalopathy. In conclusion, in an era in which biological therapies are continually evolving and expanding, knowledge about the potential neurotoxicity of these new therapies and their management becomes crucial. Although ustekinumab-induced encephalopathy is uncommon, the recognition of this potentially serious side effect is important because prompt withdrawal is associated with a favourable outcome. Whether methotrexate played an additional contributing role is currently unknown, but it is a factor that should be considered.

Keywords: Crohn's disease, encephalopathy, neurotoxicity, ustekinumab

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Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease that affects individuals of any age and sex. Approximately one-third of patients at diagnosis and over 50% during the course of the disease will suffer severe clinical manifestations leading to significant morbidity and impaired quality of life.[1,2] During the last decade, numerous therapeutic options have been developed, namely, new biologic agents such as vedolizumab and ustekinumab, that expanded the therapeutic options previously limited to corticosteroids, immunosuppressors, and anti-tumour necrosis factor (TNF) antibodies.[2]

Ustekinumab is a novel and highly effective monoclonal antibody against the p40 subunit of interleukin (IL)-12 and IL-23 that prevents binding of both ILs to the IL-12Rβ1 target receptor. Ustekinumab was initially found efficacious in the

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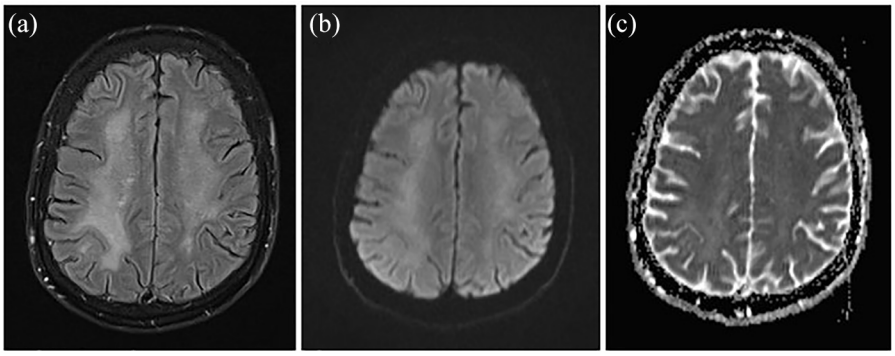

Figure 1. Brain MRI performed on admission when the patient was confused, disoriented, mentally slow and had difficulty performing skilful acts. (a) Axial FLAIR (1.5T TR 9000, TE 115) shows diffusely abnormal white matter with predominance on the right parietal part. (b) DWI image shows hyperintensity and (c) ADC (1.5T TR 7200, TE 89, b 1000) does not show restricted diffusion.

treatment of psoriasis and psoriatic arthritis and more recently in the treatment of moderate and severe active CD with a good safety profile.[3]

Ustekinumab did not show significant increase of malignancy, serious or opportunistic infections, anaphylaxis or other severe adverse events in large clinical trials.[3–6] Data from real-world clinical practice, however, are scarce and the description of potential rare adverse events that appear in this setting is important to improve patients' management.

Case report

A 48-year-old man was diagnosed with ileocolic and fistulizing perianal CD at the age of 21. He initially achieved clinical remission under corticosteroid therapy but followed a steroid-dependent course and azathioprine was introduced. Shortly after, the drug was discontinued due to development of bone marrow aplasia and hepatic veno-occlusive disease. Due to persistent CD activity, the patient received methotrexate, infliximab, adalimumab and certolizumab without improvement. In 2008, at the age of 36, he underwent autologous haematopoietic stem cell transplantation, achieving clinical and endoscopic remission. One year later, he presented endoscopic relapse and adalimumab was reintroduced initially at standard doses but in 2012 required dose intensification to 40 mg weekly and reintroduction of methotrexate 25 mg subcutaneous weekly. The patient achieved clinical response to this combination therapy until 2019, when he presented a clinical relapse and was started on ustekinumab induction with 390 mg intravenous (IV) infusion, followed by 90 mg subcutaneous at week 8, associated with a short tapering course of prednisone with an initial dose of 40 mg. Methotrexate was continued at the same dose of 25 mg subcutaneous per week.

One month after the second ustekinumab dose, when the patient was already off steroids, he was admitted due to altered mental status. The patient had been well until 1 week earlier, when he developed confusion, disorientation, mental slowness and difficulties performing skilled acts. Results of a comprehensive metabolic panel, complete blood cell count, erythrocyte sedimentation rate, C-reactive protein and a coagulation panel were within normal limits. Brain magnetic resonance imaging (MRI) revealed moderate to severe extensive symmetrical subcortical white matter hyperintensity, sparing U-fibres and cortex consistent with leukoencephalopathy without gadolinium enhancement or restricted diffusion on diffusion-weighted imaging (DWI) (Figure 1). Cerebrospinal fluid (CSF) analysis showed normal values of glucose, proteins and cell counts; blood, urine and CSF cultures and polymerase chain reaction (PCR) for *Mycobacterium*, *Tropheryma whipplei* and JC virus were negative. A right frontal brain biopsy showed a predominance of foamy histiocytic infiltrates (immunoreactive for CD68 and CD163 and negative for S-100 and CD1a) distributed in a patchy and perivascular pattern, associated with edema, diffuse astrocytic gliosis and minimal foci of necrosis in brain parenchyma. They were accompanied by a slight perivascular lymphocytic infiltrate (predominantly CD3+)

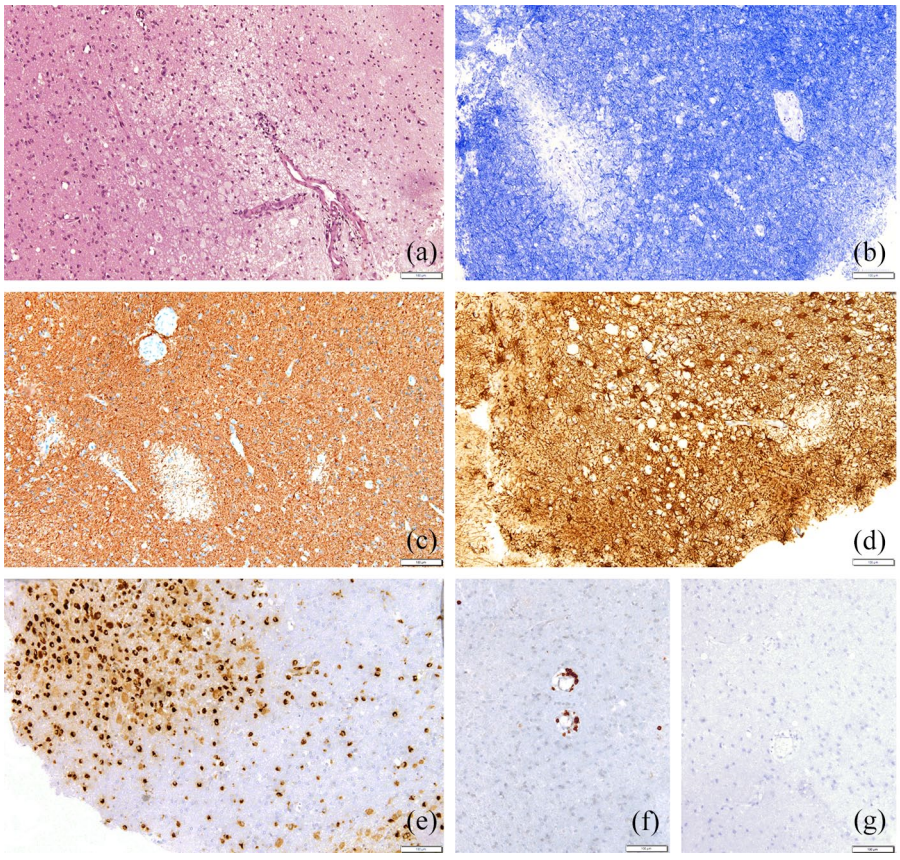

Figure 2. (a) H&E showed fragments of brain parenchyma with patchy infiltrates of foamy histiocytes, with apparent perivascular location. Luxol fast blue highlighted foci of loss of myelin (b) that were consistent with perivascular foci of axonal destruction (c) without clear signs of demyelination. (d) GFAP demonstrated a diffuse gliosis and (e) CD68 showed abundant foamy histiocytes. (f) CD3 highlighted scant perivascular T lymphocytes, (g) while the biopsy was almost devoid of B lymphocytes (CD20). All images ×100.

and luxol fast blue and neurofilament stains showed focal perivascular axonal destruction without demyelination (Figure 2). Due to rapidly evolving encephalopathy, the absence of clinical and laboratory evidence of metabolic and infectious causes and the fact that drug toxicity could not be ruled out, ustekinumab and methotrexate were discontinued and high-dose IV corticosteroids were administered (methylprednisolone 1 g/day × 5 days) with no clear improvement. In the ensuing 2 weeks, the patient became bed-ridden with spastic severe tetraparesis (left side Medical Research Council strength scale 0/5 and right side 2/5), dysphagia that required nasogastric tube for enteral feeding, aphasia and dysarthria that made him unable to obey any order and language output limited to a few unintelligible monosyllabic sounds. The patient further worsened to a state of minimal consciousness with akinetic mutism. A specific diagnostic work-up for adult-onset leukodystrophies, including blood, urine and genetic testing,[7] was performed with negative results except for the presence of a genetic heterozygous variant of unknown significance (c.1436A > T) on the *HTRA1* gene, different from the heterozygous *HTRA1* mutations associated with familial autosomal dominant small vessel disease.[8]

A new brain MRI showed a marked worsening of the leukoencephalopathy that affected the entire subcortical supratentorial white matter without gadolinium enhancement but with restricted diffusion on DWI (Figure 3). Approximately 5 weeks after the encephalopathy onset, the patient started a gradual and slow recovery. He was discharged to a neurorehabilitation centre where his neurological deficits continued to improve. At follow-up visits, 6, 12 and 18 months after admission, the patient was fully recovered and had

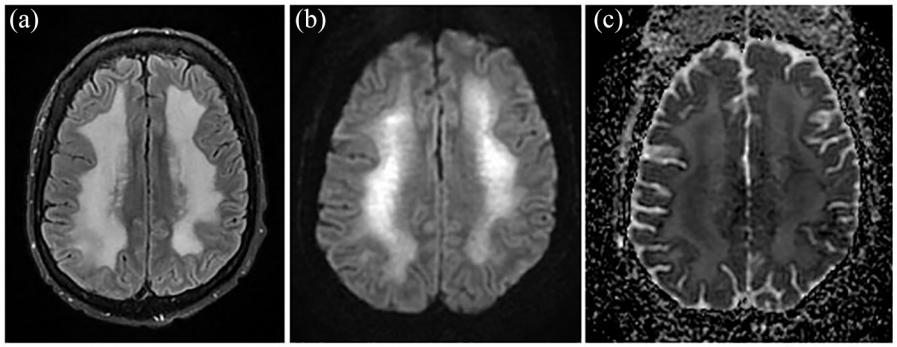

Figure 3. Brain MRI performed 7 weeks after hospital admission when the patient had a severe spastic tetraparesis, severe dysphagia and dysarthria and akinetic mutism. (a) Axial FLAIR (3T TR 9000, TE 136) shows a worsening of the abnormal white matter but sparing of grey matter and U-fibres. (b) DWI image shows increase of the hyperintensity and (c) ADC (3T TR 10508, TE 80, b 1000) shows areas with diffusion restriction.

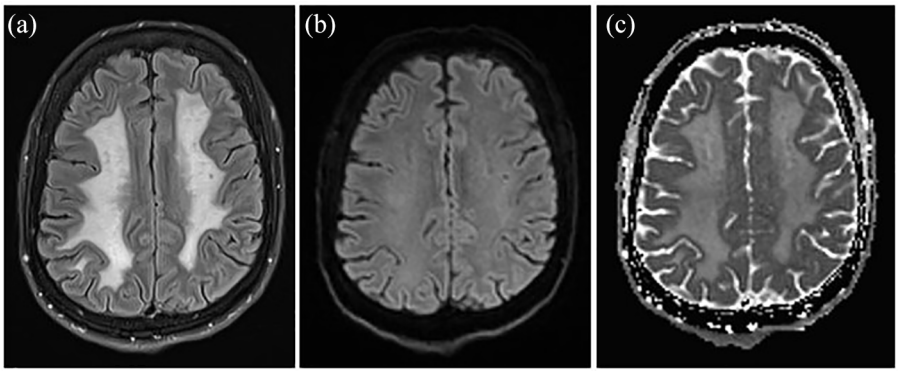

Figure 4. Brain MRI performed 6 months after hospital admission when the patient had normal physical and mental functions. (a) Axial FLAIR (3T TR 9000, TE 136) shows persistence of the FLAIR abnormality. (b) DWI image shows an almost normal intensity and (c) ADC (3T TR 10508, TE 80, b 1000) the resolution of the restricted diffusion.

returned to his previous work (computer technician). Physical and neurological (including cognitive examination) was completely normal. The family confirmed that he was 'exactly the same as before, as if nothing had happened to him'. Repeat MRI at 6 and 18 months after admission showed the persistence of the FLAIR abnormality of the white matter and complete regression of diffusion restriction (Figure 4).

Exhaustive family history revealed no relevant neurological diseases, with the exception of a subjective cognitive decline in his 71-year-old father, who has a history of active smoking, hypertension and dyslipidemia and poorly controlled diabetes. A brain MRI was performed on the patient's father and revealed moderate severity periventricular, subcortical and pontine white matter T2/FLAIR hyperintensities (Fazekas 2) that were suggestive of vascular microangiopathy and were deemed as concordant with his age and medical history.

As for the course of CD, the patient achieved clinical, biological and radiological remission after these two first doses of ustekinumab. Since then, no specific treatment for CD has been prescribed and no signs of CD activity have appeared after 18 months.

Discussion

Ustekinumab has been used for the treatment of moderate to severe cases of CD since its approval in 2016 confirming successful medical results

Table 1. Ustekinumab-related neurologic adverse events: Review of the literature.

Adverse event	No. of cases	Baseline disease	Weeks after UST initiation	Source
PRES	2 1	CD Psoriasis	1 and 2 120	Real-world case reports[15] Clinical Trial[16]
Headache (severe[a])	7 (1) 1 (1)	CD CD	Unknown Unknown	Real-world cohort[11] Real-world cohort[13]
Idiopathic intracranial hypertension	2	Psoriasis	24 and 40	Real-world case reports[17,18]
Other demyelinating diseases of the CNS	1	CD	8	Clinical Trial[10]
Thymoma-associated myasthenia gravis[b]	1	Psoriatic arthritis	24	Real-world case reports[19]
Herpetic encephalitis	1	Psoriasis	Unknown	Real-world case reports[20]
Guillain–Barré syndrome	1	CD	48	Real-world case reports[21]

CD, Crohn's disease; CNS, central nervous system; PRES, posterior reversible encephalopathy syndrome; UST, ustekinumab.
[a]Led to ustekinumab discontinuation.
[b]In a patient also taking etanercept.

even in patients who failed anti-TNF therapy.[9] Integrated data from all phase II/III ustekinumab clinical trials[9,10] and real-world cohorts on its current approved indications (psoriasis, psoriatic arthritis and CD)[11–14] have shown a favourable safety profile of the drug. So far, only a few cases of ustekinumab-related neurologic adverse events have been reported, all of them with full resolution after drug discontinuation, and leukoencephalopathy was not the presenting syndrome in any of them (Table 1).[10,11,13,15–21]

Our patient developed rapidly progressive encephalopathy with extensive confluent supratentorial white matter lesions 12 weeks after starting treatment with ustekinumab and had a slow improvement when this drug and the background treatment with methotrexate were discontinued. The temporal association and the reasonable exclusion of alternative causes strongly suggest that the encephalopathy was an adverse effect of the therapy with ustekinumab.

Neurotoxicity is very unusual in patients taking low doses of oral methotrexate.[22] Furthermore, methotrexate leukoencephalopathy is more prominent in the occipital lobes and the main histological findings are macrophagic infiltration, demyelination and fibrinoid changes in the capillaries, which are not the case in our patient.[23] Taken together, these data do not suggest that methotrexate was the causative agent of the encephalopathy, but it cannot be completely ruled out whether it had a contributory role.

In contrast to the reversible clinical manifestations, the MRI leukoencephalopathy did not regress except for the remission of the restricted diffusion, the latter indicative of cytotoxic edema. This clinical–neuroradiological discordance could indicate that the patient had a subclinical leukoencephalopathy that antedates the onset of the clinical manifestations. The causes of leukoencephalopathy include a broad differential diagnosis of demyelinating, infectious, toxic, metabolic and genetic diseases.[7,24] It is highly unlikely that previous treatments, adalimumab and oral methotrexate were the cause: Adalimumab has been associated with symptomatic demyelinating events and focal but not diffuse white matter lesions,[25] and although methotrexate can cause asymptomatic MRI leukoencephalopathy, it has been reported in the setting of IV high doses or intrathecal administration, which our patient never received.[26] Moreover, the patient had been taking low doses of methotrexate for several years and did not develop the symptoms until ustekinumab was introduced.

In our patient, the genetic study of adult-onset leukodystrophies detected a heterozygous variant of unknown significance (VUS) on the *HTRA1* gene, different from the heterozygous *HTRA1* mutations associated with the autosomal dominant cerebral small vessel disease known as CADASIL type 2.[8] The lack of family history (patient's father without stroke history or disproportionate small vessel disease for his cerebrovascular risk factors) and the age at presentation are not consistent with CADASIL type 2 that causes leukoencephalopathy, slowly progressive cognitive decline and strokes in older patients.[8,27] It is important to note that rare variants in *HTRA1* have been associated with increased white matter hyperintensity burden on MRI but with a pattern typical of small vessel disease.[28] Nevertheless, we cannot rule out whether the genetic variant of our patient on a gene associated with cerebral small vessel and white matter disease could have provided an increased susceptibility to ustekinumab-induced clinical manifestations.

In conclusion, we believe that the rapidly progressive, clinically reversible encephalopathy in our patient was caused by ustekinumab neurotoxicity and we cannot rule out as contributor factors the long-term exposure to low-dose methotrexate and the heterozygous VUS in the *HTRA1* gene. Our case suggests that patients taking ustekinumab who present with encephalopathy should be rapidly assessed, and the drug discontinued if other causes are ruled out. This fact is important, taking into account the excellent recovery of this case despite very severe neurological deficits at presentation.

Author contributions

Jordi Sarto: Conceptualization; Writing – original draft; Writing – review & editing.

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Julián Panés: Conceptualization; Supervision; Writing – review & editing.

Albert Saiz: Conceptualization; Supervision; Writing – review & editing.

Conflict of interest statement

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Patient consent

The patient gave written informed consent for publication of medical information and images.

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