CASE REPORT

Recovery from delirium and psychotic manifestations following treatment of anaemia with off-label rituximab in active cold haemagglutinin disease

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SUMMARY

Anaemia is an independent, commonly under-recognised risk factor for delirium. Prompt management of anaemia and its underlying aetiology could result in recovery from delirium and associated psychotic manifestations. We report this unprecedented case of complete recovery from delirium and challenging behaviour, following treatment of autoimmune haemolytic anaemia with rituximab.

BACKGROUND

Cold haemagglutinin disease (CHAD) is rare and accounts for 15% of autoimmune haemolytic anaemia.¹ It predominantly affects women, and is immunoglobulin M (IgM)-mediated in 90% of cases.^{1 2} Anaemia is an independent risk factor for delirium with a higher prevalence at lower haemoglobin levels.³ We present a case of complete resolution of delirium and marked improvement in psychotic behaviour following the off-label use of rituximab to control haemolytic anaemia.

CASE PRESENTATION

An 83-year-old man presented to the emergency department following collapse. A diagnosis of lower respiratory chest infection (LRTI) was made and he was transferred to the Older Persons Unit (OPU).

He was diagnosed with CHAD 4 years prior and lymphoplasmacytic lymphoma (LPL) confirmed by bone marrow examination a year before this presentation. Non-small cell lung carcinoma remained in remission 8 years after treatment and a left-sided temporal meningioma remained stable under conservative management. He also had a history of diet-controlled type 2 diabetes, folate deficiency (on replacement) and osteoarthritis (on regular paracetamol and, when required, tramadol).

Challenging behaviour in the Haematology Day Unit had limited his management to symptomatic support with transfusions (8–10 units/month over 8 months prior to admission). His occasionally paranoid behaviour had also triggered a Community Mental Health Team assessment almost a year prior to his admission. He lived alone in a flat and had a carer daily to assist him with meal preparation as he was independent with personal care. He was also driving after he managed to regain his license, given his diagnosis of cerebral meningioma. He was an ex-smoker and no history of excess alcohol intake was elicited.

On initial assessment in the OPU, the patient was more agitated, inattentive and, occasionally, more aggressive to staff members. He was displaying some paranoid ideas (fixating on financial abuse by his relatives) and inappropriate behaviours (self-harming episodes and urinating in wrong places). His carer also confirmed the acute onset of this new presentation, which was different from his usual personality. Therefore, he was clinically diagnosed with delirium and he was also Confusion Assessment Method (CAM)-positive on routine assessment. He had splenomegaly and an IgM paraprotein while virology screening revealed previous hepatitis B virus (HBV) infection. Despite good recovery from his LRTI, he remained delirious for 5 weeks following his admission and initial antibiotic treatment. The hospital's Old Age Psychiatry team attributed this impulsive, self-harming behaviour to the meningioma and a personality disorder. However, subsequent CT brain imaging did not reveal any acute meningioma changes; and any explanation regarding the amplification of his previously known personality disorder remained elusive.

INVESTIGATIONS

One week post-completion of the patient's antibiotic regimen, his haemoglobin was 46 g/L (42 g/L on admission; normal 130–170 g/L), white cell count $4.8 \times 10^9/L$ ($6.7 \times 10^9/L$ on admission; normal $4\text{--}11 \times 10^9/L$), neutrophils $2.8 \times 10^9/L$ ($3.2 \times 10^9/L$ on admission, normal $2\text{--}7.5 \times 10^9/L$) and platelets $142 \times 10^9/L$ ($150 \times 10^9/L$ on admission, normal $150\text{--}440 \times 10^9/L$). C reactive protein was 20 mg/L (69 mg/L on admission, normal <10 mg/L), lactate dehydrogenase levels 515 U/L (normal 135–225 U/L) and IgM levels 16.5 g/L (normal 0.5–2.0 g/L) with a new IgM- κ band in the β region. He had normal renal and liver profiles. His basic delirium screen, including thyroid function, folate, vitamin B₁₂ and corrected calcium levels, were all normal, and syphilis serology was negative. HBsAg (surface antigen) was negative, HBcAbs (core antibodies) was positive with a viral load (HBV DNA) <20 IU/mL suggestive of a previous HBV infection. CT of the brain confirmed the unchanged meningioma and was negative for acute ischaemic changes and for subdural haematoma. A CT chest, abdomen and pelvis scan was also performed, which only showed an enlarged spleen and uncomplicated diverticulosis. The patient also had a normal chest X-ray and negative urine examination.

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Figure 1 Unfilled triangles represent onset of unconjugated hyperbilirubinemia and expression of challenging behaviour. Following confirmation of unconjugated hyperbilirubinemia, total bilirubin measurements were used for monitoring the haemolytic process. Black diamonds represent index admission, and onset of delirium and aggressive manifestations; black triangles represent recovery of delirium and aggressive behaviour. Rituximab induction therapy (3 doses) is represented by black arrows, while maintenance therapy (2 doses) is represented by white arrows. Grade 3 neutropenia ($0.8 \times 10^9/L$) induced after the third dose of rituximab (curved-down arrow). Small and large curved-up arrows represent grade 2 ($1.2 \times 10^9/L$) neutropenia and normal ($3.0 \times 10^9/L$) neutrophils, respectively.

DIFFERENTIAL DIAGNOSIS

A wide differential diagnosis is usually applicable in most cases of delirium and especially in older people, where the underlying mechanism may be multifactorial. Infection, which had initially been thought to trigger the delirium in our case, resolved promptly. No deliriogenic drugs (anticholinergics, antipsychotics, anticonvulsants, antidepressants and/or anxiolytics) were administered during this period. The patient was infrequently taking tramadol before this admission, but no opiates were administered while in hospital. Metabolic causes, such as hyperglycaemia and hypoglycaemia, hypercalcaemia, hyponatremia and hypernatremia, uraemia, thyroid dysfunction and vitamin deficiencies, were all ruled out. The patient did not have a history of excessive alcohol intake. He remained well hydrated while in hospital as he was independent with personal care. CT of the brain did not show any significant cerebrovascular disease, subdural haematoma, hydrocephalus and/or change in the size of his known meningioma to explain his delirious presentation. Constipation, bladder function and pain were persistently monitored during admission, and no issues were identified.

TREATMENT

On OPU, the patient's challenging behaviour was managed with 'one-to-one' nursing, with good effect. Haloperidol was available to be administered in the event of more aggressive presentations, as suggested by the Psychiatric Liaison Team, but it was only administered once.

The patient had grade 4 haemolytic anaemia requiring 13 blood units transfused over 40 hospital days. In view of his ongoing significant transfusion requirements, he started intravenous rituximab 375 mg/m²/week over 4 weeks with anti-HBV prophylaxis. Following his initial 5-day course of antibiotics (coamoxiclav), no further antibiotics were prescribed as there was no clinical evidence of infection and his inflammatory markers were unremarkable.

OUTCOME AND FOLLOW-UP

The patient's haemoglobin count markedly improved after the third dose of rituximab. The infusions, however, were

interrupted as he developed grade 3 neutropenia (figure 1). On discharge to a Mental Health Unit, he had not required blood transfusion for 4 weeks. Five months after his delirium onset, he re-attended the Haematology Day Unit, where he was CAM negative on routine screening with complete resolution of his CHAD. He started outpatient maintenance rituximab given the improvements in his LPL and CHAD. At 6 months after initial therapy, he has no evidence of HBV reactivation, his haemoglobin and neutrophil levels are normal (figure 1), he has not been transfused for over 6 months and the improvement in his behaviour is maintained.

DISCUSSION

The majority of monoclonal-IgM-CHAD cases are associated with an underlying B-cell lymphoproliferative disorder, most commonly LPL (75%).² Single-agent rituximab treatment of CHAD can achieve overall and complete response rates of 57% and 21%, respectively, while around 50% LPL cases respond.¹ Anaemia-associated delirium can potentially be mediated through reduced oxygen delivery to brain tissue.^{3 4} This mechanism is different to the neurotropic effect of vitamin B₁₂ in patients with pernicious anaemia.⁵

In our case, challenging behaviour became evident on presentation of haemolytic anaemia almost a year prior to onset of

Learning points

- ▶ This case emphasises the importance of considering anaemia as one of the potentially reversible causes in the management of delirium.
- ▶ Routine assessment and optimisation of anaemia should be included in the comprehensive review of patients with geriatric oncology.
- ▶ Novel treatments may have additional, unexpected benefits on the outcome of complex cases. This, however, needs further clarification.

delirium (figure 1). Delirium did not resolve following recovery from sepsis, but only after the patient's haemolytic anaemia was treated and haemoglobin was significantly improved using off-label rituximab. An important confounding factor to be considered is the potentially beneficial effect that the rituximab therapy may have had in resolving delirium by suppressing the autoimmune inflammatory process involved in CHAD. Finally, care delivered in the Mental Health Unit may have further improved and stabilised this patient's psychiatric outcomes.

Contributors MKA collected data and drafted the manuscript. SR collected data. DW was involved in revising the manuscript critically. MKi was responsible for conception of the case report and gave final approval of the version to be published.

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REFERENCES

- 1 Owen RG, Pratt G, Auer RL, *et al*. Guidelines on the diagnosis and management of Waldenström macroglobulinaemia. *Br J Haematol* 2014;165:316–33.
- 2 Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. *Blood* 2013;122:1114–21.
- 3 Joosten E, Lemiengre J, Nelis T, *et al*. Is anaemia a risk factor for delirium in an acute geriatric population? *Gerontology* 2006;52:382–5.
- 4 Moghaddam B, Schenk JO, Stewart WB, *et al*. Temporal relationship between neurotransmitter release and ion flux during spreading depression and anoxia. *Can J Physiol Pharmacol* 1987;65:1105–10.
- 5 Zucker DK, Livingston RL, Nakra R, *et al*. B12 deficiency and psychiatric disorders: case report and literature review. *Biol Psychiatry* 1981;16:197–205.

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