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Severe Anaemia during Natalizumab Treatment: Case Presentation with Literature Review

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Abstract

Progressive multifocal leukoencephalopathy is the most common serious complication related to natalizumab. However, serious haematological complications are very uncommon during treatment with natalizumab. Here we reported the case of an 18-year-old man with a 4-year history of relapsing-remitting multiple sclerosis. He was treated firstly by Teriflunomide for 1 year, but he presented relapses and his MRI shows new contrast-enhancing lesions. Therefore, we decided to switch from Teriflunomide to Natalizumab. The patient presented with profound anaemia after the 16th infusions treatment with Natalizumab. The patient's hemoglobin was 3.2 g/dL with a lower blood reticulocyte value. After red cell transfusions and cessation of Natalizumab, anaemia resolved. Natalizumab was changed by an anti-CD20 monoclonal antibody. The patient had a stable course of multiple sclerosis at 13 months after initiation of Rituximab. We should alert clinicians to be aware of the possibility of anaemia during treatment by Natalizumab.

Keywords

Anaemia, Erythroblasts, Haematological Monitoring, Multiple Sclerosis, Natalizumab

1. Background

Natalizumab (NTZ) is the first efficacious monoclonal antibody approved for relapsing-remitting multiple sclerosis (RRMS) in 2010, likely in highly active forms [1]. It is also used in active inflammatory bowel disease [2] [3]. The overall incidence of adverse events associated with NTZ is low. This treatment's known serious adverse effect is progressive multifocal leukoencephalopathy caused by John

Cunningham Virus (JCV) [1]. Severe anaemia may not be recognized as an adverse effect of NTZ treatment, and its cause remains unclear. In this case report, we describe this rare complication of NTZ treatment, with a literature review.

2. Case Report

Mr. T. A is an 18-year-old man with a 4-years history of RRMS, but no other notable medical history. He was treated firstly by Teriflunomide for 1 year, which was switched to monthly Natalizumab infusion, due to lack of efficacy since April 2019. The patient remained clinically and radiographically stable during NTZ treatment. In July 2020, 3 weeks after the 16th NTZ infusions, the patient developed severe fatigue, shortness of breath, palpitation, and vertigo with no haemorrhagic syndrome and no fever. Physical examination revealed pallor and tachycardia (110 bpm).

Laboratory testing revealed profound normocytic normochromic anaemia with hemoglobin at 3.2 g/dL and a lower blood reticulocyte value (1785/mm^3), with no abnormalities in lymphocytes (6840/mm^3) or in platelet counts (324,000/mm^3). Erythroblasts precursors were absent. Sternal puncture revealed hypercellular marrow with the presence of many signs of dyserythropoiesis, megaloblasts with pearl chromatin, multinucleated erythrocytes, interchromatin bridges, images of cells in mitosis and karyorrhexis. Vitamin B12, folic acid, and iron levels were normal. Parvovirus serology was negative. The erythrocyte sedimentation rate, Reactive C Protein (RCP), serum bilirubin, and serum lactate dehydrogenase (LDH) were normal. There were no splenomegaly or mass lesions in total body CT scans. Bone marrow aspirate was not done.

We, therefore, ruled out myeloproliferative disease and diagnosed severe anaemia from possible drug toxicity (NTZ). We discontinued NTZ treatment and the patient was treated by blood transfusions. Haemoglobin was at 9.7 g/dL five days after transfusion. The patient had complete recovery of all clinical symptoms of anaemia.

We switched from NTZ to an anti-CD20 monoclonal antibody (Rituximab) considered as another second-line therapy in MS, with rapid action delay, to avoid the risk of rebound effect at 7 weeks to the last infusion of NTZ. Anaemia resolved and haemoglobin was 14 g/dL after 2 months NTZ discontinuation. The patient had a stable course of RRMS 18 months after initiation of Rituximab, without the appearance of a new episode of anaemia.

3. Discussion

Multiple sclerosis (MS) is one of the most frequent neurological diseases and it is a cause of disability among the young population [1]. The therapeutic arsenal in the disease-modifying therapy of MS, especially in its relapsing-remitting form, is becoming richer. The news drugs are characterized by the varying mechanisms of action and the potentially higher efficacy on the inflammatory component of the disease.

NTZ is a humanized monoclonal antibody that is used for the treatment of highly active MS since 20 years, with better control of disease activity. Except for PML, the pivotal studies of NTZ did not demonstrate severe adverse events with haematological safety profile and do not recommend any haematological monitoring [1]. A post-marketing prospective study assessing of incidence of hematologic side effects during NTZ treatment, included 66 patients, revealed a high occurrence of hyperlymphocytosis (48%) and hypereosinophilia and low risk of anaemia 6% (4 patients) [4]. Some case reports of severe anaemia during NTZ treatment have been also described, but it is extremely rare, we found only 3 cases in the literature [5] [6] [7].

The physiopathology of aneamia with NTZ is unknown. NTZ is a humanized monoclonal antibody directed against α-4 β1-integrin expressed by leucocytes (VLA-4). NTZ thus inhibits the adhesion of lymphocytes to endothelial vascular cell adhesion molecules and prevents their migration into the central nervous system.

VLA-4 is also known expressed on erythroblasts, hence NTZ may inhibit erythropoiesis and maturation of erythroblast and lead to the appearance of erythroblast in peripheral blood (PB) [8]. The erythroblast appearance in PB, may explain a previous case of severe anemia, and it has been described as a reversible adverse effect of NTZ treatment [8] [9].

The immune-mediated acute haemolytic anaemia is another reported possible mechanism of anaemia during NTZ treatment [4]. Hemolytic anemia was ruled out in our patient.

To our knowledge, this is the 4th case of Natalizumab-induced severe anaemia reported so far in the literature (**Table 1**) [5] [6] [7]. The age of the 3 patients was around 50, whereas our patient was younger. In the first case reported in 2012, the anemia had appeared after the first infusion [5], whereas in the 2 following cases with ours the anemia had appeared beyond the fifteenth infusion. The hemoglobin level was variable in the 3 cases and the lowest in our case.

Table 1. Cases of severe aneamia during NTZ treatment in the literature with our case.

	Gender/ Age (years)	Number of infusions of NTZ	Hemoglobin	Management	Treatment switch
Midaglia 2012 [5]	F/50	1	5.4 g/dL	Transfusions, Intravenous immunoglobulin and steroids	NA
Simone 2014 [6]	F/51	34	7.3 g/dL	Transfusions, Discontinued NTZ	NA
Seibert 2015 [7]	F/49	15	7.4 g/dL	3 monthly blood transfusions Discontinued NTZ	NA
Our Case	M/18	16	3.2 g/dL	Transfusions, Discontinued NTZ	Rituximab

Management of anemia in all cases was based on blood transfusion and discontinuation of NTZ therapy. The evolution was favorable in all 4 cases.

4. Conclusion

Fatigue is a frequent symptom of MS but it can also be related to anaemia secondary to DMTs. Despite the rarity of this haematological complication with NTZ, it seems feasible to regularly monitor blood cell count to optimize treatment safety in an individualized approach.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Clerico, M., *et al.* (2017) Long-Term Safety Evaluation of Natalizumab for the Treatment of MS Expert Opinion on Drug Safety. *Expert Opinion on Drug Safety*, **16**.

[2] Nelson, S.M., Nguyen, T.M., McDonald, J.W. and MacDonald, J.K. (2018) Natalizumab for Induction of Remission in Crohn's Disease. *Cochrane Database of Systematic Reviews*, **8**. https://doi.org/10.1002/14651858.CD006097.pub3

[3] Park, S.C. and Jeen, Y.T. (2018) Anti-Integrin Therapy for Inflammatory Bowel Disease. *World Journal of Gastroenterology*, **24**, 1868-1880. https://doi.org/10.3748/wjg.v24.i17.1868

[4] Bresch, S., Cohen, M., Rocher, F., Laffon, M., Thomas, P. and Lebrun, C. (2012) Anomalies hématologiques du natalizumab et sa signification Clinique. *Revue Neurologique*, **168**, 116-120.

[5] Midaglia, L., Rodriguez Ruiz, M. and Muñoz-García, D. (2012) Severe Haematological Complications during Treatment with Natalizumab. *Multiple Sclerosis*, **18**, 1644-1646. https://doi.org/10.1177/1352458512442262

[6] Simone, A.M., Ferraro, D., Vitetta, F., Marasca, R., Bonacorsi, G., Pinelli, G., Federzoni, L., Nichelli, P.F. and Sola, P. (2014) Severe Anemia in a Patient with Multiple Sclerosis Treated with Natalizumab. *Neurology*, **83**, 374-375. https://doi.org/10.1212/WNL.0000000000000614

[7] Seibert, J.B. and Alvarez, E. (2015) Severe Anemia in a Patient with Multiple Sclerosis Treated with Natalizumab. *Neurology*, **84**, 861. https://doi.org/10.1212/01.wnl.0000461938.49936.52

[8] Kobayashi, Y., Takamatsu, R., Sato, S., Watanabe, R., Hoshi, K., Ishii, W. and Yahikozawa, H. (2019) Erythroblast Appearance Associated with Natalizumab. *Multiple Sclerosis and Related Disorders*, **29**, 145-147. https://doi.org/10.1016/j.msard.2019.01.041

[9] Li, W., Guo, R., Song, Y. and Jiang, Z. (2021) Erythroblastic Island Macrophages Shape Normal Erythropoiesis and Drive Associated Disorders in Erythroid Hematopoietic Diseases. *Frontiers in Cell and Developmental Biology*, **8**, 613885. https://doi.org/10.3389/fcell.2020.613885