CASE REPORT

Severe immune thrombocytopaenia in a patient taking benznidazole for chronic Chagas disease

Clara Crespillo-Andújar,¹ María Calbacho Robles,² Francesca F Norman,³ Jose A Pérez-Molina³¹National Referral Unit for Tropical and Travel Medicine, Department of Internal Medicine, Hospital Universitario La Paz-Carlos III, IdiPAZ, Madrid, Spain²Department of Hematology, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain³National Referral Centre for Tropical Diseases, Infectious Diseases Department, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain

Correspondence to

Dr Clara Crespillo-Andújar, clara.crespillo@gmail.com

Accepted 10 March 2018

SUMMARY

Chagas disease is a parasitic disease that mostly affects Latin American countries, but it has currently become a worldwide epidemic due to migration. Both drugs marketed for its treatment (benznidazole and nifurtimox) are associated with a high rate of adverse reactions. Benznidazole is preferred initially because of its more favourable toxicity profile and perceived greater efficacy. Hypersensitivity dermatological reactions, gastrointestinal and neurological disturbances represent the most common drug-related adverse events. General symptoms such as fever, arthralgia, myalgia or bone marrow depression (leucopaenia) are seen less frequently. We describe the case of a 33-year-old woman with chronic Chagas disease who presented with acute gingival bleeding and severe thrombocytopaenia, probably related to benznidazole treatment. Temporal association with drug initiation and recovery after treatment withdrawal were demonstrated. Clinicians should be aware of the possible association between immune thrombocytopaenia and benznidazole, even though the pathogenesis remains unclear at present.

BACKGROUND

Chagas disease, caused by the parasite *Trypanosoma cruzi*, is transmitted in endemic areas through blood-sucking triatomine insects of the subfamily Triatominae. Other routes of infection are vertical transmission, the ingestion of contaminated food or beverages, through transfusion of contaminated blood and blood products, organ transplantation or laboratory accidents.^{1–3} This parasitic disease affects almost 6 million people in Latin America, but as a consequence of migration, it has currently become a global epidemic.^{4–6}

There are only two marketed drugs for the treatment of Chagas disease: benznidazole and nifurtimox. Benznidazole is usually the first choice given its better tolerability and perceived greater efficacy. It is administered orally during 60 days at daily doses of 5 mg/kg.^{1–3 7 8} Unfortunately, benznidazole has a high rate of adverse events and treatment discontinuations that range from 10% to 87%^{9 10} and 4% to 41.5%,^{11 12} respectively. Main side effects are hypersensitivity skin reactions, gastrointestinal disorders, peripheral neuropathy and general symptoms such as anorexia, asthenia and myalgia. Less frequent adverse events include hypertransaminasemia,

bone marrow depression, fever and arthritis.^{13–17} Leucopaenia (most frequently neutropenia and rarely agranulocytosis) is the most common toxic haematological effect.^{18–20}

We present the case of a 33-year-old woman who developed severe thrombocytopaenia with gingival bleeding and petechiae in the context of benznidazole treatment for chronic Chagas disease. This case report highlights a very infrequent adverse reaction associated with benznidazole and focuses on the importance of complete history taking and examination in the diagnostic process.

CASE PRESENTATION

A 33-year-old Bolivian woman presented to the emergency department in May 2015 with acute gingival bleeding. She had been diagnosed with Chagas disease 3 years previously and had been taking benznidazole at a dose of 5 mg/kg of body weight per day divided in two daily doses (300 mg twice daily) for the previous 15 days. She had no other medical history or drug allergies. She had been living in Spain since 2003 and had not left the country since then. Clinical examination revealed petechial lesions in the oral mucosa and gingival bleeding. There were no other cutaneous lesions and cardiorespiratory examination and blood pressure were normal.

INVESTIGATIONS

The first blood test revealed a low haemoglobin level with microcytic and hypochromic red blood cells and extremely low platelet counts ($1 \times 10^9/L$). Table 1 summarises initial and follow-up blood test results. A blood smear confirmed the presence of severe thrombocytopaenia with no abnormal cells. Chest radiograph was normal.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of thrombocytopaenia includes several causes with diverse pathophysiological mechanisms (platelet destruction or consumption, dilution or redistribution and insufficient production secondary to bone marrow disorders) which may occur at the same time. For this case, various causes were considered:

► Infections: Numerous viral infections can cause thrombocytopaenia through a variety of mechanisms. Thrombocytopaenia normally appears during the acute phase of the disease, recovering spontaneously when the infection resolves and

To cite: Crespillo-Andújar C, Calbacho Robles M, Norman FF, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223788

Table 1 Full blood counts, coagulation assays and patient management

Date	Haemoglobin (g/L)	White cell count ($\times 10^9/L$)	Platelet count ($\times 10^9/L$)	INR	eGFR (CKD-EPI) ml/min	ALT/AST	Treatment
31/03/2015	12.6	4.69	203			13/10	
19/04/2015							BNZ 300 mg twice daily
04/05/2015 HA	11.9	4.46	1	1	118.9	16/12	BNZ withdrawal Start of prednisone 100 mg daily
05/05/2015	11.7	4.36	1	1.1	122.3	15/13	Prednisone 100 mg daily
06/05/2015	11.2	7	27	1.1	121.6	13/10	Prednisone 100 mg daily
07/05/2015 HD	11.2	7.14	73				Prednisone 90 mg daily
13/05/2015	11.4	7.99	467	1.1	118.9	11/9	Prednisone 60 mg daily
20/05/2015	11.1	7.85	403				Prednisone 60 mg daily
27/05/2015	11.3	7.60	254				Prednisone 30 mg daily
10/06/2015	12.0	6.55	276		123.1	18/15	Prednisone 15 mg daily 7 days and PDD
01/07/2015	12.1	5.26	218				Suspension
09/09/2015	13.3	5.85	251		121.6	19/16	

ALT/AST, alanine transaminase/aspartate transaminase; BNZ, benznidazole; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; HA, hospital admission, HD, hospital discharge, PDD, progressive descending doses.

may occur due to bone marrow suppression and/or due to immune-mediated processes, such as during dengue virus²¹ or cytomegalovirus infections.²² It could also be the initial manifestation of HIV infection. The mechanism may be complex as ineffective platelet production (possibly due to infection of megakaryocytes) and an increase of peripheral platelet destruction occur.²³ Among patients with chronic hepatitis C virus (HCV) infection, thrombocytopenia can be persistent and the pathophysiology is multifactorial (autoimmunogenicity, direct bone marrow suppression, hypersplenism and decreased platelet production).²⁴ Positive viral serology and/or the presence of a positive PCR for the virus are diagnostic in these cases and the peripheral blood smear is typically normal.

Bacterial sepsis can also cause thrombocytopenia by direct bone marrow suppression and platelet destruction, and this may be associated with disseminated intravascular coagulation (DIC).²⁵

Intracellular parasites may also cause thrombocytopenia. Severe *Plasmodium falciparum* malaria is a common cause of coagulopathy and thrombocytopenia, secondary to DIC,²⁶ as is babesiosis, which can also cause thrombocytopenia secondary to hypersplenism and DIC in severe cases.²⁷

- Hypersplenism and chronic liver disease with portal hypertension can capture platelets causing mild to moderate thrombocytopenia.²⁸ Radiological confirmation of hypersplenism is needed in these cases.
- Microangiopathic processes combine diffuse microvascular coagulation and/or thrombosis and can occur due to congenital or acquired diseases. In this case, platelets are consumed in thrombi. Signs of haemolytic anaemia are present in the peripheral blood smear (schistocytes), and lactate dehydrogenase determination is useful to follow the intensity of haemolysis.
- Myelodysplastic syndromes are acquired bone marrow disorders that are associated with impaired haematopoiesis.

These syndromes can be progressive (leukaemia) and are often associated with other abnormalities in cellular blood counts and presence of cell dysplasia or immature cells in the peripheral blood smear and bone marrow.²⁹

- Immune thrombocytopenia (ITP) is a common cause of acquired thrombocytopenia in which there are no abnormalities of other cell lines (leukocytes and erythrocytes). It is caused by platelet destruction mediated by autoantibodies against platelet antigens.³⁰ It may be primary or associated with other conditions, such as infections, autoimmune diseases, or drug exposure (drug-dependent antibody-mediated platelet destruction). Anti-platelet antibodies are rarely detected, so testing for these has no clinical utility.³¹ ITP is a presumptive diagnosis in cases where the physical examination and laboratory data do not suggest an alternative aetiological diagnosis. In drug-dependent thrombocytopenia, there is a temporal relationship between drug exposure and platelet count decrease. The interval between drug initiation and onset of thrombocytopenia is generally less than 2 weeks and spontaneous recovery is usually observed 1 week after treatment is withdrawn.
- The antiphospholipid syndrome may be associated with thrombocytopenia. The clinical spectrum includes thromboembolic disease and pregnancy-related morbidity. Positive laboratory tests for anticardiolipin antibodies or lupus anticoagulant present in plasma are needed for diagnosis.³²

Peripheral blood smear was used in this case to discard most of the previous potential diagnoses. The patient did not have a previous history of chronic diseases and baseline blood tests, including coagulation assays, before benznidazole initiation were normal. Serology for hepatotropic viruses (such as HCV and HBV) and HIV were negative. After discarding other secondary causes, the patient was diagnosed with drug-induced Immune thrombocytopenia (DITP) secondary to treatment with benznidazole.

TREATMENT

As a first measure, benznidazole was immediately discontinued (after 15 days of treatment). As ITP and DITP cannot be initially distinguished, the patient was admitted to hospital and high-dose glucocorticoid treatment (prednisone at a dose of 1.5 mg/kg) was started and maintained for 4 days with subsequent tapering of doses.

OUTCOME AND FOLLOW-UP

After treatment discontinuation and with high-dose oral glucocorticoid therapy, the patient improved and was asymptomatic and clinically stable during hospitalisation allowing hospital discharge after 4 days, with a progressive improvement in platelet counts. Additional immunosuppressive treatment was not required and prednisone, at progressively descending doses, was maintained for 2 months. The patient remained asymptomatic during a 2-year follow-up, and treatment with benznidazole or other trypanocidal nitroimidazole derivatives was not reintroduced because of the high risk of toxicity.

DISCUSSION

ITP is an acquired thrombocytopaenia due to autoantibody-mediated destruction of platelets. Diagnosis is mainly based on clinical history, physical examination, complete blood count, peripheral smear and the exclusion of other causes of thrombocytopaenia.^{30 33} There are no reliable laboratory tests to confirm the diagnosis. Assays for antibodies to specific platelet glycoproteins are not routinely recommended because they are not present in all ITP patients and they could be elevated in other causes of non-immune thrombocytopaenia.³⁴ ITP could be primary or secondary to some conditions, such as infections, or other haematological or autoimmune diseases. Our patient had a negative screen for viral infections (HIV, HCV and HBV) and thyroid function tests were normal. Bone marrow biopsy was not considered necessary, as dysplasia was absent in the peripheral smear and the patient had a good clinical outcome with recovery of blood parameters with the performed management. The patient had been living in Spain since 2003 and had not returned to Bolivia, and this limited the differential diagnosis as certain non-endemic diseases in Spain, such as dengue or malaria, could be excluded.

When drug-dependent platelet antibodies mediate the platelet destruction, the syndrome is named DITP. There are several theories about how the immune thrombocytopaenia is developed in the presence of certain drugs (or their metabolites): classic drug-dependent platelet antibodies (quinine, etc), hapten-induced antibodies (penicillin, etc), fibronectin-dependent antibodies (tirofiban, etc), G_{IIb/IIIa}-binding monoclonal antibodies (abciximab, etc), drug-induced autoantibody formation (procainamide, etc) and immune complex formation (heparin, etc).³⁵ Some drugs are more likely to cause thrombocytopaenia than others.³⁶ Clinically, thrombocytopaenia may present with skin and/or mucosal purpuric lesions with a platelet nadir of less than $10 \times 10^9/L$. Bleeding risk is inversely related to the platelet count, although patients with profound thrombocytopaenia occasionally have no bleeding symptoms. Regarding management, the suspected responsible drug must be discontinued and hospitalisation should be considered in severe cases or in patients with overt bleeding for which platelet transfusions may be necessary.³⁵ Even though there is no evidence supporting the efficacy of glucocorticoid therapy in DITP, these are usually prescribed as this entity may not be readily distinguished initially from ITP. Platelet counts usually increase after drug discontinuation and sensitivity to the drug will persist indefinitely.³¹

In this case, the patient had been taking benznidazole treatment for 15 days and had a very low platelet nadir (with a normal count before starting benznidazole) that improved with treatment withdrawal. Even if confirmation was not possible, the timeline of events supported the diagnosis and benznidazole was not reintroduced after recovery.³⁷ Benznidazole has not been included in the database of drugs associated with DITP,^{36 38} and to our knowledge, there is only one previous case described in the literature of benznidazole-related DITP. A 58-year-old woman taking benznidazole, at a dose of 400 mg day presented with an oral petechial rash and haemorrhagic mucosal blisters after 11 days of treatment. Platelet nadir was $6 \times 10^9/L$ and after benznidazole withdrawal and 7 days of oral prednisone treatment, values returned to normal.²⁰

The exact mechanisms of direct benznidazole toxicity and associated immune-mediated thrombocytopaenia remain unclear. Benznidazole is a nitroheterocyclic compound that must undergo nitroreductase-mediated activation to produce the reactive metabolites responsible for its parasitocidal effect.^{39–41} The reactive metabolites (free radicals) that are formed during the bioactivation process may be toxic,⁴⁰ and these metabolites may play an important role in the mechanism of DITP.

In conclusion, the management of patients with thrombocytopaenia should always include careful history taking (including details of all medication taken by the patient) and a complete physical examination. For the diagnosis of ITP, a complete blood count and peripheral blood smear are necessary accompanied by other diagnostic tests that could exclude other aetiological causes. If a new drug has been introduced recently, it is essential to consider treatment withdrawal if DITP is suspected.

Learning points

- ▶ Benznidazole could be associated with severe immune thrombocytopaenia, although currently the underlying mechanism remains unclear.
- ▶ Immune thrombocytopaenic purpura is an acquired thrombocytopaenia mediated by autoantibody platelet destruction that can be primary or secondary to other causes.
- ▶ If the destruction is caused by drug-dependent platelet antibodies, it is named drug-induced immune thrombocytopaenia.
- ▶ Both are diagnoses of exclusion so a complete medical history (focusing on the medication taken by the patient) and physical examination are essential.

Contributors JAP-M, FFN and MCR were involved in management of the patient. CC-A wrote the first draft of the manuscript. JAP-M, FFN and MCR reviewed and edited the manuscript. All of the authors have seen and approved the final text.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 WHO. *Control of Chagas disease: second report of the WHO expert committee: WHO technical report series*. Geneva: World Health Organization, 2002:905.
- 2 Bern C. Chagas' disease. *N Engl J Med* 2015;373:456–66.
- 3 Pérez-Molina JA, Molina I. Chagas disease. *The Lancet* 2018;391:82–94.

- 4 WHO. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. *Wkly Epidemiol Rec* 2015;90:33–43.
- 5 Manne-Goehler J, Umeh CA, Montgomery SP, et al. Estimating the burden of Chagas disease in the United States. *PLoS Negl Trop Dis* 2016;10:e0005033.
- 6 Requena-Méndez A, Aldasoro E, de Lazzari E, et al. Prevalence of Chagas disease in Latin-American migrants living in Europe: a systematic review and meta-analysis. *PLoS Negl Trop Dis* 2015;9:e0003540.
- 7 Dias JC, Ramos AN, Gontijo ED, et al. [Brazilian consensus on chagas disease, 2015]. *Epidemiol Serv Saude* 2016;25:3–60.
- 8 Coura JR, de Abreu LL, Willcox HP, et al. [Comparative controlled study on the use of benznidazole, nifurtimox and placebo, in the chronic form of Chagas' disease, in a field area with interrupted transmission. I. Preliminary evaluation]. *Rev Soc Bras Med Trop* 1997;30:139–44.
- 9 Sosa Estani S, Segura EL, Ruiz AM, et al. Efficacy of chemotherapy with benznidazole in children in the indeterminate phase of Chagas' disease. *Am J Trop Med Hyg* 1998;59:526–9.
- 10 de Pontes VM, Souza Júnior AS, Cruz FM, et al. [Adverse reactions in Chagas disease patients treated with benznidazole, in the State of Ceará]. *Rev Soc Bras Med Trop* 2010;43:182–72010.
- 11 Yun O, Lima MA, Ellman T, et al. Feasibility, drug safety, and effectiveness of etiological treatment programs for Chagas disease in Honduras, Guatemala, and Bolivia: 10-year experience of Médecins Sans Frontières. *PLoS Negl Trop Dis* 2009;3:e488.
- 12 Levi GC, Lobo IM, Kallás EG, et al. Etiological drug treatment of human infection by *Trypanosoma cruzi*. *Rev Inst Med Trop Sao Paulo* 1996;38:35–8.
- 13 Viotti R, Vigliano C, Lococo B, et al. Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment: a nonrandomized trial. *Ann Intern Med* 2006;144:724–34.
- 14 Morillo CA, Marin-Neto JA, Avezum A, et al. Randomized trial of benznidazole for chronic Chagas' cardiomyopathy. *N Engl J Med* 2015;373:1295–306.
- 15 Molina I, Salvador F, Sánchez-Montalvá A, et al. Toxic profile of benznidazole in patients with chronic chagas disease: risk factors and comparison of the product from two different manufacturers. *Antimicrob Agents Chemother* 2015;59:6125–31.
- 16 Pinazo MJ, Guerrero L, Posada E, et al. Benznidazole-related adverse drug reactions and their relationship to serum drug concentrations in patients with chronic Chagas disease. *Antimicrob Agents Chemother* 2013;57:390–5.
- 17 Aldasoro E, Pinazo MJ, Oliveira I, et al. Arthritis and benznidazole: more closely related than we thought. *Antimicrob Agents Chemother* 2015;59:727–9.
- 18 Pinazo MJ, Muñoz J, Posada E, et al. Tolerance of benznidazole in treatment of Chagas' disease in adults. *Antimicrob Agents Chemother* 2010;54:4896–9.
- 19 Sosa-Estani S, Armentani A, Araujo G, et al. [Treatment of Chagas disease with benznidazole and thioctic acid]. *Medicina* 2004;64:1–6.
- 20 Dias JCP, Coura JR. *Clínica e terapêutica da doença de Chagas: uma abordagem prática para o clínico geral*. SciELO Books 1997:1–490.
- 21 La Russa VF, Innis BL. Mechanisms of dengue virus-induced bone marrow suppression. *Baillieres Clin Haematol* 1995;8:249–70.
- 22 Yaari S, Koslowsky B, Wolf D, et al. CMV-related thrombocytopenia treated with foscarnet: a case series and review of the literature. *Platelets* 2010;21:490–5.
- 23 Ballem PJ, Belzberg A, Devine DV, et al. Kinetic studies of the mechanism of thrombocytopenia in patients with human immunodeficiency virus infection. *N Engl J Med* 1992;327:1779–84.
- 24 Dahal S, Upadhyay S, Banjade R, et al. Thrombocytopenia in patients with chronic hepatitis C virus infection. *Mediterr J Hematol Infect Dis* 2017;9:e2017019.
- 25 Greco E, Lupia E, Bosco O, et al. Platelets and multi-organ failure in sepsis. *Int J Mol Sci* 2017;18:2200.
- 26 Lacerda MV, Mourão MP, Coelho HC, et al. Thrombocytopenia in malaria: who cares? *Mem Inst Oswaldo Cruz* 2011;106 Suppl 1:52–63.
- 27 Akel T, Mobarakai N. Hematologic manifestations of babesiosis. *Ann Clin Microbiol Antimicrob* 2017;16:903.
- 28 Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. *J Clin Invest* 1966;45:645–57.
- 29 Li W, Morrone K, Kambhampati S, et al. Thrombocytopenia in MDS: epidemiology, mechanisms, clinical consequences and novel therapeutic strategies. *Leukemia* 2016;30:536–44.
- 30 Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med* 2002;346:995–1008.
- 31 Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med* 2007;357:580–7.
- 32 Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *Journal of Thrombosis and Haemostasis* 2006;4:295–306.
- 33 Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011;117:4190–207.
- 34 Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010;115:168–86.
- 35 Arnold DM, Nazi I, Warkentin TE, et al. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. *Transfus Med Rev* 2013;27:137–45.
- 36 Arnold DM, Kukawadia S, Nazi I, et al. A systematic evaluation of laboratory testing for drug-induced immune thrombocytopenia. *J Thromb Haemost* 2013;11:169–76.
- 37 Aster RH, Curtis BR, McFarland JG, et al. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. *J Thromb Haemost* 2009;7:911–8.
- 38 Drug-Induced Immune Thrombocytopenia. Results of the testing for drug-dependent platelet-reactive antibodies by the bloodcenter of Wisconsin (1995-2015). 2017. http://www.ouhsc.edu/platelets/InternetPostingLab2_18_11Frames.htm (accessed Nov 2017).
- 39 Wilkinson SR, Kelly JM. Trypanocidal drugs: mechanisms, resistance and new targets. *Expert Rev Mol Med* 2009;11:e31.
- 40 Castro JA, de Mecca MM, Bartel LC. Toxic side effects of drugs used to treat Chagas' disease (American trypanosomiasis). *Hum Exp Toxicol* 2006;25:471–9.
- 41 Rajão MA, Furtado C, Alves CL, et al. Unveiling benznidazole's mechanism of action through overexpression of DNA repair proteins in *Trypanosoma cruzi*. *Environ Mol Mutagen* 2014;55:309–21.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow