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PHOTO QUIZ

A man with 'black fingers'

M.A. de Witte[1,3]*, R.M. Determann[2], S.S. Zeerleder[1,4]

Departments of [1]Haematology, [2]Internal Medicine, Academic Medical Centre, Amsterdam, the Netherlands, [3]Department of Hematology, University Medical Center Utrecht, the Netherlands, [4]Department of Immunopathology, Sanquin Research, Amsterdam, the Netherlands, *corresponding author, e-mail: m.a.dewitte-7@umcutrecht.nl

In December, a 76-year-old male presented himself to the emergency room with 'black, painful fingers', which had developed within days. The patient had no prior medical history. He had no specific complaints, was not taking any medicine and had no intoxications. Physical examination of the hands showed a black discoloration on digits II-V of both hands with a relatively sharp demarcation at the 2nd phalanges. Laboratory tests of the blood were hampered due to direct 'clotting' of the blood in the test tubes.

Figure 1. *Hands showing black discoloration on digits II-V*

WHAT IS YOUR DIAGNOSIS?

See page 39 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 35)

A MAN WITH 'BLACK FINGERS'

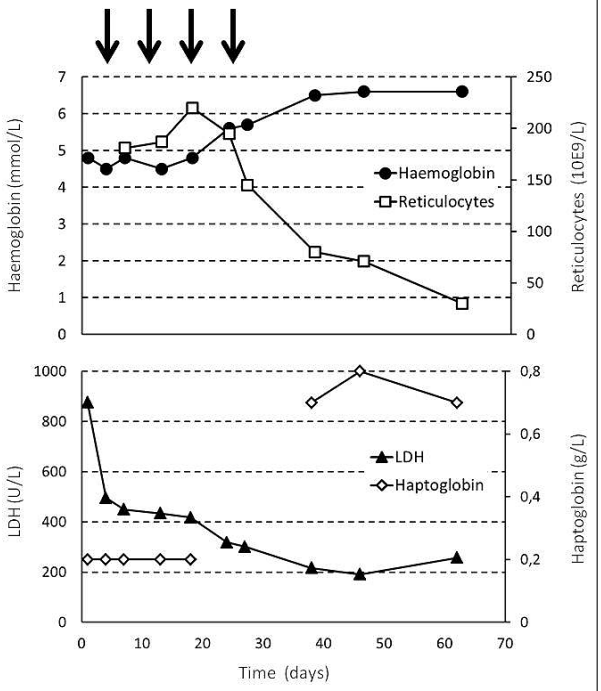
DIAGNOSIS

The apparent 'clotting' of the blood immediately after collection at room temperature was strongly suggestive of either the presence of cryoglobulins or cold agglutinins. Indeed, by pre-analytic handling and performing the laboratory tests at 37° C, agglutination could be avoided. These laboratory tests revealed the following: haemoglobin 4.8 mmol/l; leucocytes 14.4 10^9/l; reticulocytes 181.4 10^9/l; lactate dehydrogenase 877 U/l; haptoglobulin <0.2 g/l; and direct bilirubin 38 µmol/l. The direct antiglobulin test was strongly positive for C3d and negative for immunoglobulins (anti-IgG/IgM/IgA). An autoantibody with an anti-I specificity was found. No cryoglobulins were detected. Based on the clinical picture characterised by acrocyanosis and autoimmune haemolytic anaemia (AIHA) in the presence of cold antibodies, the diagnosis of cold agglutinin disease (CAD) was made.

CAD is a rare disease, which is either idiopathic (often precluding an occult lymphoma) or secondary to a haematological malignancy or infection (mycoplasma/EBV).[1] Cold antibodies are IgM auto-antibodies which bind to red blood cells at temperatures below 37° C. These antibodies are frequently directed against the antigen 'I', a carbohydrate structure present on red blood cells. Incidental cold agglutinins (polyclonal) can be found at a fairly high incidence, often with a benign nature. In CAD the optimal binding temperature of IgM auto-antibodies covers a broad range (broad thermal amplitude). In patients suffering from CAD, exposition of extremities to temperatures around the optimal binding temperature of the autoantibodies (e.g. around 30° C) may result in red blood cell agglutination in the microcirculation, a phenomenon which becomes clinically apparent by Raynaud's phenomenon and acrocyanosis. The closer the thermal amplitude shifts towards 37° C, the higher is the chance and efficacy of complement activation and hence the complement-mediated haemolysis.[2]

The basic rule in treatment of CAD is 'keep-it-warm'. Usually, patients with CAD suffer from a mild anaemia and there is no need for correction. However, when anaemia is more severe, treatment depends on the underlying cause. In case of an infection, CAD is often self-limiting. In CAD secondary to a haematological disease, this disease should be treated. For an idiopathic CAD, optimal treatment strategies have not been defined. Steroids and splenectomy – fairly effective in AIHA caused by warm auto-antibodies – have shown little effect in CAD.[3] Several small studies have shown a beneficial effect of rituximab in about 50% of the patients with CAD; although relapses frequently occur (usually within a year).[4,5] Addition of fludarabine seems to improve the response rate significantly, but toxicity can by considerable.[6]

Figure 2. *Haematological response after the administration of rituximab (depicted by arrows)*



In this patient a small (3%) monoclonal B cell population (IgM kappa) was detected. Given the serious acrocyanosis and ongoing haemolysis (*figure 2*) in the absence of an overt lymphoma, we chose to treat this patient with four doses of rituximab. After a month, the haemolysis halted (*figure 2*) and the haemoglobin level increased. The IgM kappa M protein was undetectable. In addition, the acrocyanosis did not expand further. Unfortunately, however, the pre-existing acrocyanosis was so severe that the upper phalanges could not be rescued and needed to be amputated.

This case demonstrates that haemolysis and acrocyanosis caused by cold antibodies in a patient with an underlying monoclonal B cell population can be halted by rituximab. Moreover, this case illustrates that the proper diagnosis in

CAD requests appropriate pre-analytic handling of patient samples.

REFERENCES

1. Zeerleder S. Autoimmune haemolytic anaemia – a practical guide to cope with a diagnostic and therapeutic challenge. Neth J Med. 2011;69:177-84.
2. Swiecicki PL, Hegerova LT, Gertz M. Cold agglutinin disease. Blood. 2013;122:1114-21.
3. Berentsen S. How I manage cold agglutinin disease. Br J Haematol. 2011;153:309-17.
4. Berentsen S, Ulvestad E, Gjertsen BT, et al. Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. Blood. 2004;103:2925-8.
5. Schöllkopf C, Kjeldsen L, Bjerrum OW, et al. Rituximab in chronic cold agglutinin disease: a prospective study of 20 patients. Leuk Lymphoma. 2006;47:253-60.
6. Berentsen S, Randen U, Vågan AM, et al. High response rate and durable remissions following fludarabine and rituximab combination therapy for chronic cold agglutinin disease. Blood. 2010;116:3180-4.