When winter is coming, you better keep warm

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SUMMARY

A 75-year-old patient presented with fluctuating swelling around the eyes, vasculitis at the lower legs and back of the upper legs and an extreme hypogammaglobulinaemia. An extensive work-up revealed the presence of secondary immunoglobulin M cryoglobulinaemia related to a monoclonal B-cell lymphocytosis. Precipitation of proteins also resulted in a decreased C1-esterase inhibitor causing angioedema. She was treated with an elderly chronic lymphocytic leukaemia regimen consisting of obinutuzumab and chlorambucil with a subsequent clinical and haematological remission.

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INTRODUCTION

Detection of a monoclonal protein is frequent, and haematologists mostly focus on the underlying B-cell clone that produces this protein. Regardless of the size of the clone, the protein produced can be very toxic, resulting in different clinical presentations such as light-chain amyloidosis, monoclonal immunoglobulin deposition disease, crystal-storing histiocytosis and monoclonal cryoglobulinaemia. A small B-cell clone can therefore result in a serious and life-threatening condition, and a fast reduction of the monoclonal protein must be pursued.[1]

CASE PRESENTATION

A 75-year-old Caucasian female was seen at the haematology consultations at the end of November. The patient was in her usual state of health until seven months prior to consultation when she suffered from an upper airway infection. Coinciding with this upper airway infection she reported swelling around the eyes. Her family doctor prescribed an anti-cough syrup. She consulted an ophthalmologist who didn't notice anything special at the time of consultation and provided natural tears. One week later, a diffuse rash appeared, most pronounced at the lower legs. The rash was documented as urticarial, most likely due to the recent viral infection. During the summer, the rash waxed and waned together with the swelling around the eyes. In October, she started to gain weight, her legs were swollen. The rash on the lower legs became more intense and did not fade out as it used to do earlier. She contacted her family doctor who performed a blood test and noticed extreme hypogammaglobulinaemia. Her family doctor referred her for a haematology consult.

At the consultation, the patient did not mention any fever or night sweats. She gained 5 kg during the last 4 weeks. Her lower legs and ankles were painful and swollen, it was often difficult to walk. No other arthralgia were mentioned, she had no trouble eating and did not suffer from respiratory or abdominal complaints. Bilateral swelling around the eyes came more frequent and lasted longer as compared to previous months, whereas her vision was perfect. She had a history of hypertension and a total hip replacement. Apart from spironolactone she did not take any medication.

On clinical examination, we found a discrete swelling around the eyes without change in colour, sclerae were normal and no swelling of the tongue was seen. The lower legs were intense red and swollen (*Figure 1*). At the back of the upper legs, red macules were found (*Figure 2*). Further clinical examination was normal.

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FIGURE 1. Vasculitis at the lower legs at first presentation.

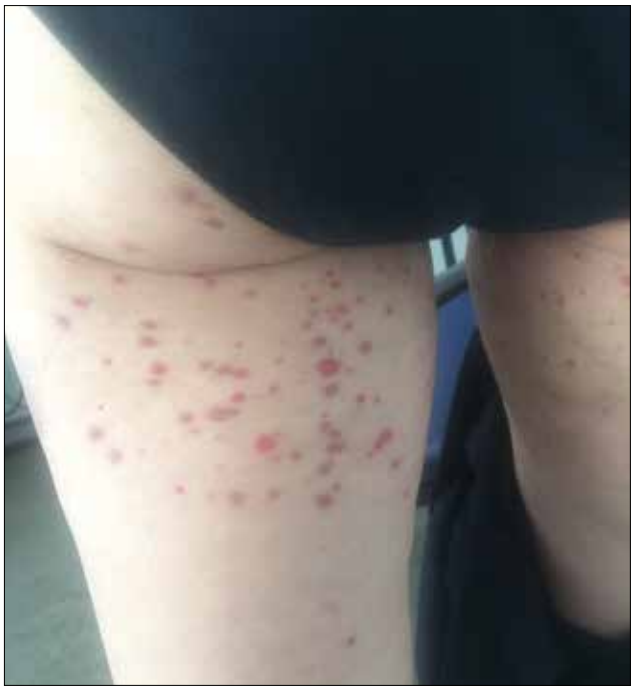

FIGURE 2. Macules at the back of the upper legs at first presentation.

INVESTIGATIONS

Extensive laboratory testing confirmed the hypogammaglobulinaemia; anti-nuclear factor, anti-neutrophil cytoplasm antibodies and rheumatoid factor were negative; complement C3 and C4 were extremely low. Cellular haematology and clotting tests were normal, urinary sediment was negative, there was no proteinuria.

Protein electrophoresis showed the presence of a monoclonal immunoglobulin M (IgM) protein and kappa light chains of 354 mg/l (nl 3.3-19.4) with a free light chain ratio (kappa/lambda) of 35.76 (nl 0.26-1.65). C1 esterase-inhibitor was 0.19 (nl 0.25-0.41). Flow cytometry documented a small B-cell clone in peripheral blood (0.525 x 10E9/L) with positivity for CD19, CD20, CD22, CD23, CD43, CD79b, FMC7, CD200 and kappa light chain restriction. The population was only partially positive for CD5 and showed no positivity for CD10, CD11c and CD103, resulting in a Catovsky score of 2/5.[2]

A biopsy of the skin was taken and demonstrated leucocytoclastic vasculitis.

PET/CT did not show any fluorodeoxyglucose-avid lesions. A trephine biopsy and marrow aspirate was performed in which the same monoclonal B-cell population was found, plasma cells were below 1%. There were no arguments for Waldenström's disease, MYD88 mutation analysis was not performed.

Testing for cryoglobulins was positive and showed monoclonal IgM kappa cryoglobulins.

DIAGNOSIS

We concluded to a new diagnosis of secondary type I cryoglobulinaemia with C1-esterase inhibitor insufficiency caused by the presence of an IgM secreting monoclonal B-cell lymphocytosis (MBL).

TREATMENT

We started treatment three weeks after the first haematology consultation. The moment she started treatment, the skin lesions were changed to diffuse macules and target lesions (*Figure 3*).

We treated the patient with an elderly chronic lymphocytic leukaemia regimen consisting of obinutuzumab and chlorambucil aiming for a fast reduction in monoclonal protein.[3] Corticosteroids were added and tapered during the first cycle. Having completed three cycles, the patient demonstrated a clinical remission (*Figure 4*), no monoclonal population was found in the blood, and C1-esterase inhibitor levels had returned to normal values. We stopped treatment after five cycles due to development of leukopenia.

DISCUSSION

Cryoglobulinaemia is a rare disorder resulting in diffuse precipitation of immunoglobulins at low temperatures. This causes a systemic inflammation with often related skin and renal complications. Due to a snowball effect of the immunoglobulin precipitate, other proteins such as the C1-esterase

FIGURE 3. Target lesions at the start of treatment.

FIGURE 4. Clinical remission following three cycles of obinutuzumab/chlorambucil.

inhibitor can be markedly decreased. Cryoglobulinaemia is most frequently seen as type II or III disease, often in association with hepatitis C virus. Type I cryoglobulinaemia, in which only a monoclonal fraction is involved, only accounts for 10-15% of patients.[4] There is a general female predominance in a 3:1 ratio. Protein electrophoresis of our patient only showed a marked decrease in immunoglobulins, no immune fixation was performed in the first analysis. The presence of a monoclonal B-cell population and the slightly positive testing for cryoglobulinaemia raised suspicion of a monoclonal protein. A second sample with a closer look at the immunoglobulins revealed a monoclonal IgM protein and confirmed the presence of IgM kappa cryoglobulins. In two recent series of type I cryoglobulinaemia of 36 and 64 patients, the underlying cause was monoclonal gammopathy of undetermined significance (MGUS) in 36% and 43% respectively while the others suffered from a malignant haematological malignancy.[5,6] Since the monoclonal protein came with clinical implications, those patients suffering from MGUS should now be called (monoclonal gammopathy of clinical significance (MGCS) patients.[7]

IgM cryoglobulinaemia appears to be more related with skin involvement, whereas IgG cryoglobulinaemia is more preluded for kidney involvement. It must be underlined that only symptomatic patients were included in the abovementioned series. Néel *et al*. identified 227 patients through laboratory databases of whom 191 had no clinical manifestations and were not treated.[5] Our patient presented with a monoclonal B-cell lymphocytosis. In the two series, only one and two patients respectively presented with chronic lymphocytic leukaemia. No MBL patients were documented. Our recent publication showed the rare need for treatment in MBL patients.[8] Focusing on different treatment regimens, the series of Terrier *et al*. documented a response to rituximab in 80% of patients.[6] Thalidomide and lenalidomide showed an efficacy rate of 83%, and bortezomib-based regimens were shown to be effective in 86% of treated patients. Néel *et al*. concluded that response was more consistent with the use of polychemotherapeutic regimens in contrast to single agent alkylating or single agent rituximab strategies.[5] Mortality was low in the two series and both concluded that older age and nephropathy were independently associated with a poorer survival with infection as the leading cause of death.

During the first two weeks of treatment, the rash in our patient faded, but following the infusion on day 15 of the first cycle, the patient reported a remarkable flare-up of symptoms just after leaving the hospital. Since flare-up appeared after the third full dose of obinutuzumab, this was most likely due to the rather cold infusion of obinutuzumab and not a treatment related flare-up as seen in Waldenström's macroglobulinaemia. The following infusions were administered at 37 °C using a blood heater without further complications. After establishing the diagnosis, the mysterious

KEY MESSAGES FOR CLINICAL PRACTICE

1. **The relevance of a small B-cell clone is determined by the behaviour of the monoclonal protein that is secreted.**
2. **Cryoglobulinaemia type I is a rare disorder that demands treatment if presented with symptomatic disease. Cutaneous involvement is the most frequent clinical manifestation.**
3. **Different B-cell depleting strategies come with high remission rates, the choice of regimen depends on the underlying disease.**
4. **Survival rates at 5 and 10 years are around 90% and negatively influenced by older age and kidney involvement at presentation. Infection is the leading cause of death.**

pattern of macules at the back of the upper legs remained unsolved. With further questioning, the patient told us she always waited for the bus on an iron bench, because she could not stand due to the pain in her legs and ankles. This might be an answer to the question why she presented with skin lesions at the back of the upper legs at the first consultation.

CONCLUSION

This is the first patient documented with MBL-related type 1 cryoglobulinaemia that demanded treatment due to severe vasculitis and angioedema. A B-cell depleting regimen using obinutuzumab and chlorambucil resulted in a clinical and biochemical remission.

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