A man experiencing episodes of worsening facial swelling

Commentary by
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For patients with the rare immunological syndrome acquired angioedema associated with C1 inhibitor deficiency, replacement therapy with plasma-derived C1 INH concentrate is standard treatment. For those who develop resistance to replacement therapy, another drug has been shown to be successful in managing acute episodes.

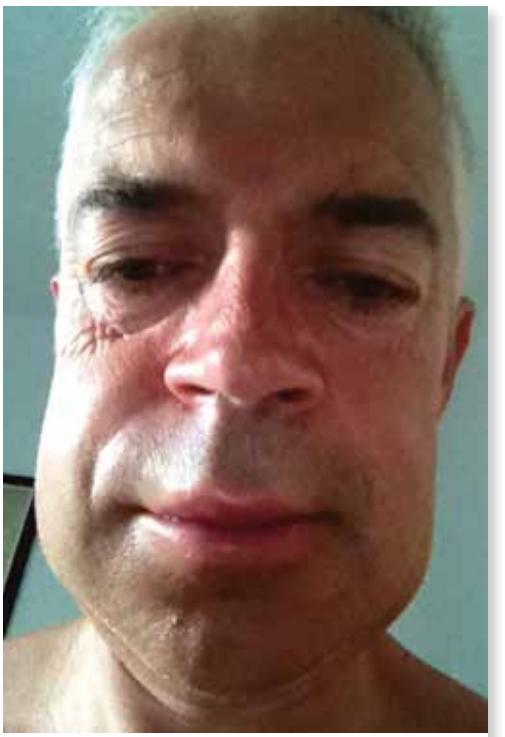

Figure. The case patient's facial swelling.

CASE PRESENTATION

Chris, a 55-year-old man, presented to his GP with a 12-month history of recurrent and increasingly frequent and severe episodes of facial swelling (Figure). The swelling would usually develop rapidly during the night and could last up to three to four days. It was not associated with a rash and was unresponsive to antihistamines. The swelling attacks were not painful and the patient did not feel generally unwell. On the most recent of these episodes, he had developed groin swelling at the same time as facial swelling.

The patient had been previously well. Prior to the onset of these facial swellings, he had experienced no lifestyle or dietary change. He was taking no medications and he had no past personal history or family history of any allergic or autoimmune disorder.

Chris was referred for immunological assessment.

What could be the cause of this patient's swelling episodes?

Consultant's comment

Chris is experiencing episodes of angioedema. The differential diagnosis of his angioedema includes:

- histaminergic angioedema
- angioedema mediated by bradykinin (as seen in ACE inhibitor-induced angioedema), and
- acquired angioedema (AAE), a rare syndrome that is frequently associated with malignancy – most commonly, lymphoproliferative disorders.

DIAGNOSIS AND INITIAL MANAGEMENT

Blood tests were ordered for Chris. The results revealed an IgM monoclonal antibody with normal IgG and IgA levels. His C4 level was markedly reduced and his C1 inhibitor (C1 INH) level was low, and there was a strongly positive alpha C1 INH antibody level (titre >1/1000).

A diagnosis of AAE secondary to monoclonal gammopathy of undetermined significance (MGUS) was made. His subsequent attacks were treated with plasma-derived C1 INH concentrate and he responded well.

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Consultant's comment

C1 INH deficiency in AAE results from increased C1 INH catabolism caused by anti-C1 INH neutralising autoantibodies associated with lymphoproliferative disorders, including MGUS and non-Hodgkin's lymphoma. Reduced C1 INH function leads to activation of the classical complement pathway and contact system, which results in raised bradykinin levels, increased vascular permeability and angioedema.[1]

The clinical presentation of AAE is broadly similar to that of hereditary angioedema (HAE). However, involvement of the face and limbs is more frequent in AAE. Patients with AAE have no family history of the disorder (the majority of patients with HAE have a family history), and symptom onset is usually after the fourth decade of life (it is usually evident by the second decade in HAE).[2]

Replacement therapy with plasma-derived C1 INH concentrate is standard treatment for attacks of AAE. Initially, this is given to treat individual episodes of angioedema, but if such episodes become very frequent then replacement therapy may be given regularly as prophylaxis.

FURTHER MANAGEMENT

Chris returned to the care of his GP with a note from the specialist advising of his diagnosis. Because he had a possibility of further attacks of AAE, he was also given a letter explaining his need for infusions of C1 INH concentrate to treat any future significant attacks of swelling. He could present the letter at a hospital emergency department to avoid treatment with adrenaline and antihistamines and delay of effective management.

Chris remained well for the next five weeks but then developed a more severe attack of facial swelling one night. This time the swelling extended into his mouth and neck, causing some airway compromise. On this occasion he responded poorly to treatment with the C1 INH concentrate infusion and required a repeat infusion within 24 hours at a much higher concentration. His immunologist was urgently consulted.

Consultant's comment

The lack of response to standard treatment indicates that Chris has developed resistance to the plasma-derived C1 INH concentrate. This occurs in some patients with AAE and is possibly due to C1 INH autoantibody development.[3]

Fortunately, there is another treatment option, icatibant, that can be offered to Chris. Icatibant, a selective bradykinin B2 receptor antagonist, is indicated for the symptomatic treatment of acute attacks of HAE in adults with C1 INH deficiency and has been used successfully (off label) in patients with AAE. Unlike plasma-derived C1 INH, icatibant is not affected by the presence of anti-C1 INH autoantibodies, which makes it a suitable treatment in patients with AAE who no longer respond to C1 INH treatment.[4] It is likely to remain effective, even with repeated use.

Icatibant is used as on-demand treatment. It has a much shorter half-life than plasma-derived C1 INH concentrate, so it is not suitable as prophylactic therapy.

FOLLOW UP

Chris's AAE has remained responsive to on-demand icatibant. He administers icatibant himself as a subcutaneous injection into the abdomen when he feels an attack starting (usually between 2 am and 4 am).

He asks whether he can expect to develop any side effects from his treatment. He is also concerned about the association between AAE and lymphoproliferative disorders and he has questions about his need for ongoing monitoring.

Consultant's comment

In clinical trials conducted in patients with HAE, icatibant has generally been a very well tolerated medication.[5] Injection site reactions were the most commonly reported side effect, with most other side effects being similar in frequency to those in control groups.[5]

Chris will need regular follow up and monitoring indefinitely. The possibility of developing Waldenstrom's macroglobulinaemia is at a rate of approximately 1.5% per year for patients with IgM MGUS.[6] In addition, IgM MGUS may progress to IgM myeloma, but this is infrequent.[6] There is also a risk of progression to lymphoma or a related malignancy; the size of this risk is related to the concentration of the serum M protein at the time of diagnosis of the IgM paraprotein. MT

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COMPETING INTERESTS: Professor Katelaris is a principal investigator in trials of icatibant and C1 INH concentrate in patients with hereditary angioedema.