



ENDGAMES

CASE REVIEW

A curious case of facial swelling in the night-time

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A 57 year old woman presented to the emergency department with swelling of the lips and oropharynx of one hour's duration. Treatment for anaphylaxis was started but 30 minutes later she was much worse. After intubation, she was taken to the intensive care unit for airway management.

She had attended the emergency department with similar symptoms one month earlier and had been treated with chlorphenamine and discharged home with an EpiPen. A referral to the allergy clinic was made.

Her medical history included hypertension, although she had never received an angiotensin converting enzyme inhibitor. In addition, two years earlier she had been diagnosed with a B lymphoproliferative disorder, which was asymptomatic and under surveillance. She had no history of asthma but had reported facial swelling as a child after a bee sting. She had no known allergies, no family history of note, and took no regular drugs.

Blood tests showed haemoglobin 91 g/L (reference range 130-180), mean cell volume 78.4 fL (80-98), platelets $159 \times 10^9/L$ (150-400), total white cell count $21.9 \times 10^9/L$ (4.0-11.0), lymphocytes $8.5 \times 10^9/L$ (1.0-4.0), and tryptase 1.45 µg/L (0-11.4).

A complement screen showed C1q 49 mg/L (50-250), C2 2.0 mg/L (14-25), C3 0.8 g/L (0.88-2.01), C4 <0.03 g/L (0.16-0.47), and C1 esterase inhibitor 54 mg/L (220-390).

Questions

1. How would you interpret the blood results?
2. What is the diagnosis?
3. What could be the underlying cause?
4. What is the treatment?

Answers

1. How would you interpret the blood results?

Answer

The low C2, C4, and C1q values are indicative of complement C1 esterase inhibitor deficiency. She also had microcytic anaemia.

Discussion

Complement is a major component of innate immunity. It mediates various pathways involved in the immune response, including the classical, alternative, and lectin pathways, which are activated in various inflammatory or infective processes.

C1-C4 are components of the classical pathway and are often low when the pathway is activated. C3 and C4 are the most commonly measured components.

The identification of low complement values can help pinpoint certain diagnoses, including acquired or inherited forms of complement deficiency, some types of haemolytic anaemia, and recurrent infections.^{1 2}

C1 esterase inhibitor is a protease inhibitor that inhibits spontaneous activation of complement. It is also one of the acute phase proteins and can be raised during inflammation. It has inhibitory roles in various other pathways, including the clotting and fibrinolytic pathways.^{3 4}

C1 esterase inhibitor deficiency results in inappropriate complement activation. This leads to consumption of the classical complement components—specifically C1, C2, and C4—as well as the release of bradykinin, which mediates vascular permeability.⁵⁻⁸

C1 esterase inhibitor deficiency is characterised by recurrent episodes of angio-oedema. It can be classified as inherited or acquired and manifests as submucosal and subcutaneous swellings in any part of the skin, gastrointestinal tract, or respiratory tract.^{9 10}

2. What is the diagnosis?

Answer

C1 esterase inhibitor deficiency.

Discussion

The vascular reaction that causes angio-oedema occurs in the deeper layers of the skin and mucous membranes. It involves localised dilatation and permeability of blood vessels. This results in tissue swelling, which is often painful but rarely pruritic. It is caused by a temporary rise in vascular permeability, which is mediated by histamine and bradykinin.^{11 12}

A study of angio-oedema without urticaria found that 16% of cases were related to a specific factor (such as food, insect bites, allergens), 7% were related to an autoimmune disease or infection, 11% were related to the use of angiotensin converting enzyme inhibitors, and 25% could be attributed to C1 inhibitor deficiency (7% of these were thought to be acquired). In addition, 3% were part of a generalised oedema syndrome and 38% had unknown causes.¹³

There are two forms of C1 esterase inhibitor deficiency—hereditary and acquired. Hereditary angio-oedema—an autosomal dominant condition with a prevalence of 1/50 000—is characterised by recurrent episodes of angio-oedema without pruritus or urticaria. The condition usually manifests before 15 years of age.¹⁴

By contrast, acquired angio-oedema presents in older patients and can be associated with various other diseases. It has a prevalence of 1/100 000 to 1/150 000,¹⁵ and was first described in 1972.¹⁶ Both forms of the disease have similar symptoms.

The swellings tend to affect the upper respiratory or gastrointestinal tracts and can cause fatal laryngeal oedema or intestinal obstruction. Attacks are often precipitated by a stimulant, such as an episode of infection or trauma.

Low serum C4 and C1 esterase inhibitor values can be diagnostic of, or help confirm, acquired angio-oedema,⁹ although C4 can be normal in between attacks.¹⁷⁻¹⁹ A normal C4 value in a patient who is experiencing an angio-oedema attack is highly suggestive of an alternative diagnosis.¹²

Acquired angio-oedema has been characterised into two types:

- Type 1: low C1 esterase inhibitor; often seen in lymphoproliferative or paraneoplastic syndromes
- Type 2: presence of autoantibodies to C1 esterase inhibitor; seen in connective tissue disorders.

The two types overlap considerably however, and some studies have shown that this differentiation is neither helpful nor necessary.²⁰⁻²³ In addition, evidence suggests that all patients with acquired angio-oedema should be tested for autoantibodies to C1 esterase inhibitor.²⁴

The course of disease is variable, with attacks ranging from being very rare to monthly.²⁵

Time to diagnosis also varies widely, and a recent UK audit showed that although diagnosis has improved it can still be up to 10 years before a diagnosis is made. Patients with acquired disease tend to experience a shorter diagnostic delay because of the association with haematological cancer and subsequent referral to secondary care services.²⁶ The average time to diagnosis of acquired angio-oedema is 2.3 to 2.48 years.^{21 27}

3. What could be the underlying cause?

Answer

The association between acquired angio-oedema and lymphoproliferative disorders (particularly B cell ones) is well recognised, and the patient's known B cell disorder may have been the underlying cause.

Discussion

A considerable proportion of patients with acquired angio-oedema have an underlying B cell disorder, and various reports have discussed this association.^{25 28} Numerous factors were taken into account when investigating this association. Patients with acquired angio-oedema have a significantly higher prevalence of monoclonal gammopathy of uncertain significance and non-Hodgkin's lymphoma.^{21 29} In addition, treatment for non-Hodgkin's lymphoma is thought to cause reversal of C1 esterase inhibitor deficiency.^{29 30}

Studies have shown that acquired C1 esterase inhibitor deficiency predisposes patients to developing non-Hodgkin's lymphoma, but lymphoproliferative disease (usually indolent lymphoma) can already be present or may develop after the onset of angio-oedema.³¹⁻³³ This risk is similar to that seen for autoimmune diseases such as rheumatoid arthritis and cryoglobulinaemia.^{34 35}

Angio-oedema can be an unusual presentation of non-Hodgkin's lymphoma, particularly when C1 esterase inhibitor values are normal, and it is worth investigating such patients for B cell lymphoproliferative disorders.²⁰

All patients with acquired angio-oedema should be monitored annually for the development of lymphoproliferative disease.³⁶ This involves a detailed history and clinical examination, focusing on the development of any B symptoms (night sweats, fever, and loss of more than 10% of body weight over six months) or lymphadenopathy. A blood screen should look for any cytopenias or a raised white cell count. About 35% of patients with acquired C1 esterase inhibitor deficiency develop monoclonal gammopathy of uncertain significance (prevalence of about 3% in people over 50 years),³⁷ but the risk of progression to multiple myeloma is the same as that seen in the general population.^{21 29}

Initially, it was thought that neoplastic lymphatic tissues used up C1 esterase inhibitor and complement, thus causing the low levels of these factors.^{28 38-40} However it is now known that antibodies against C1 esterase inhibitor can decrease the levels of activity of this enzyme even when values are normal.^{21 22}

4. What is the treatment?

Answer

Treatment should encompass both treatment of the acute attack and long term prophylaxis. Traditional treatments for anaphylaxis are ineffective in these patients.¹² Plasma derived C1 esterase inhibitor concentrate can be used in the acute setting and for prophylaxis in some instances.⁴¹

Discussion

Some patients with laryngeal oedema are resistant to plasma derived C1 esterase inhibitor concentrate and this poses a very serious problem in a potentially life threatening situation.²¹

Treatment of the underlying condition, such as a lymphoproliferative disease, often—but not always—increases C1 esterase inhibitor concentrations, thereby improving symptoms.^{24 27 29 42}

In terms of prophylaxis, antifibrinolytic agents (such as tranexamic acid) seem better than attenuated androgens (such as danazol—a 17 α -alkylated androgen), which had previously been shown to be effective in hereditary angio-oedema.^{21 43} The use of antifibrinolytics increases the risk of thromboembolism and oral anticoagulants are sometimes given concomitantly.²¹

Recent case reports have highlighted the efficacy of rituximab (an anti-CD20 monoclonal antibody) in the treatment of recurrent angio-oedema in acquired C1 esterase inhibitor deficiency.⁴⁴⁻⁴⁶ Three patients treated with rituximab for one month had a decreased incidence of angio-oedema attacks, increased concentrations of C1 esterase inhibitor, and normalised C4 values, with no adverse effects. These patients had previously needed high amounts of C1 esterase inhibitor concentrate to treat their angio-oedema.^{44 45}

Icatibant (a bradykinin B2 receptor antagonist) and ecallantide (a kallikrein inhibitor) have also been shown to be effective in the treatment of acute angio-oedema attacks.^{47 48} Icatibant can be injected subcutaneously by the patient in an emergency.⁴⁹ Ecallantide, also administered subcutaneously, is not currently licensed in the United Kingdom but has been approved by the Food and Drug Administration for use in the United States.

Most research has been done on hereditary angio-oedema type 1, but acquired angio-oedema probably responds similarly to treatment so the results can be extrapolated.⁵⁰ Regardless of whether angio-oedema is hereditary or acquired, the treatment is the same. These attacks are potentially life threatening: laryngeal attacks are associated with an overall mortality of 40%.⁵¹ Appropriate and timely diagnosis has a big impact on mortality in this condition, with mortality rates of 29% in undiagnosed patients compared with 3% in those with a diagnosis. These values refer to hereditary angio-oedema because acquired angio-oedema is so rare.⁵²

Patient outcome

Our patient recovered fully from this episode and has had no further crises to date. She does however carry icatibant (a self administered subcutaneous injection) and a C1 esterase inhibitor concentrate with her at all times. C1 esterase inhibitor concentrate is stored as a powder and needs to be reconstituted before intravenous administration in the emergency department. It is widely available in the European Union and US. Icatibant is currently available in the US and UK. After discussion at the haemato-oncological multidisciplinary team it was decided, on the basis of expert opinion, not to treat her “B cell lymphoproliferative disorder not otherwise classifiable” at present. However, this will be reconsidered if further episodes of angio-oedema occur or if she develops severe B symptoms, a doubling of white cell count in under six months, or serious anaemia or thrombocytopenia.

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