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Angioedema as a predominant symptom of *Bordetella pertussis* infection

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SUMMARY

A 41-year-old woman was referred to our hospital with a 6-week history of severe angioedema, dyspnoea and coughing. Initial investigations focused on common causes of angioedema. Clinical presentation and resistance to treatment with antihistamines and steroids made histamine-mediated angioedema unlikely. Bradykinin-mediated angioedema, such as hereditary or drug-induced angioedema, was excluded by a thorough history investigation and laboratory testing for C1-esterase and C4.

In rare cases, exogen pathogens cause angioedema. After profound testing for respiratory pathogens, *Bordetella pertussis* toxins IgA and IgG were found to be positive, indicating recent *B. pertussis* infection. Pertussis toxin may be responsible for increased vascular permeability causing angioedema. With adequate antibiotic treatment, the symptoms resolved quickly.

This case is an example of an atypical presentation of *B. pertussis* infection in an unvaccinated adult. The recent resurgence of pertussis makes early diagnosis and disease prevention by vaccination crucial.

BACKGROUND

Bordetella pertussis is a Gram-negative bacterium, and is the pathogen of the highly contagious pertussis known as ‘whooping cough’. Since 2011, the increasing incidence of pertussis despite high vaccination coverage has given rise to discussion across the world.¹ Suggested reasons for the resurgence of pertussis include higher awareness, improved diagnostic tests, emergence of new *B. pertussis* strains with greater virulence or resistance to vaccination, and rapidly waning immunity after vaccination.²

Pertussis is primarily dangerous for infants; 16 of 26 reported pertussis-related deaths in Europe in 2016 and all deaths in 2017 occurred in children younger than 3 months.^{3,4} Therefore, the focus must be placed on disease prevention, especially to reduce the risk of transmission to infants.⁵

Pertussis infection is known to proceed through three typical stages: first, catarrhal, second, paroxysmal with classic paroxysms of coughing and an inspiratory ‘whoop’ noise, and third, the convalescent stage. Adults and vaccinated patients may, however, present with mild or atypical symptoms. Here, we describe the case of an unvaccinated adult who presented with angioedema as a rare atypical symptom of *B. pertussis* infection.

CASE PRESENTATION

A 41-year-old woman was referred to the Department of Pulmonology of the Vienna General

Hospital by a local hospital with therapy-resistant dyspnoea and angioedema of unknown origin. At the first onset of dyspnoea, her local pulmonologist had her begin treatment for suspected allergic asthma with inhalative antiobstructive therapy, oral glucocorticoids and oral antihistaminergic drugs. When the symptoms did not improve, she sought help at her local hospital, where she was admitted to the pulmonology ward for 14 days without sufficient symptom control so that she was referred to our hospital.

At presentation, the patient suffered from significant swelling of her face–neck region and had a 6-week history of dyspnoea and coughing. Recently, a severe coughing attack had led to a syncope. Physical examination revealed an obese body habitus (ca. 160 cm, 85 kg) and bilateral subconjunctival haemorrhages and basal rhonchi, but no evidence of hives. The patient had stopped smoking at the onset of dyspnoea after daily consumption of 3–4 cigarettes (five pack-years). She disclosed that she was allergic to dust mites, grass and tree pollen, hay, straw, cats and dogs. No former severe illnesses were noted, apart from childhood diseases including measles, mumps, rubella and varicella. The patient was currently without employment but had formerly worked as a saleswoman.

The patient's medication included 25 mg of prednisolone once/day, 5 mg of levocetirizine as needed, inhalative budesonide two times per day, inhalative fenoterole/ipratropium bromide as needed, dihydrocodeine for coughing attacks, artificial tear eye-drops and transdermal nicotine patches. Local antimycotic treatment of laryngeal thrush, likely related to inhalative steroid treatment, with amphotericin B and nystatin had been established.

INVESTIGATIONS

Initially, routine laboratory tests, including a complete blood count with differential, and a chemistry panel with liver function, renal function, and C reactive protein (CRP) tests were performed. CRP levels were slightly elevated (0.71 mg/dL; reference range <0.5 mg/dL) at presentation at our clinic. A marked leucocytosis between 30 and 40 G/L (reference range 4.0–9.0 G/L) with relative lymphocytosis (44%; reference range 20%–40%) was seen, which gradually normalised over the course of several weeks.

Initially, the chest X-ray and head–neck/chest CT performed at the local hospital showed normal findings, apart from an enlarged thyroid gland. Further investigation showed euthyroid multinodular goitre without antibody production. Hormonal testing



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showed normal cortisol and adrenocorticotropic (ACTH) levels in the morning.

Investigations related to the initially suspected severe allergic asthma and allergic angioedema included a radioallergosorbent test (RAST), which was found to be negative for common inhalative (pollen, fungi, mites, cats, dogs and other animals) and alimentary allergens, but the total IgE was elevated to 310 kU/l (781 kU/l in the local hospital; reference range <100 kU/L). An obstructive ventilatory disorder was excluded by several lung function tests (Tiffeneau-Pinelli index 82%–86%).

Hereditary angioedema was investigated by measuring complement factor 4 (C4), which was normal (23 mg/dL and 34 mg/dL, reference range 10–40 mg/dL) and C1-inhibitor (C1-INH, C1-esterase), which measured 138% (reference range 70%–130%).

Echocardiography showed normal findings, with especially good right ventricular function.

Because of the marked leucocytosis, haemato-oncology specialists were consulted and lymphoproliferative disorders were investigated. Immunophenotyping revealed a marked absolute increase in T-cells with a normal T-cell ratio. Serum electrophoresis showed no evidence of paraproteins. Abdominal sonography and head–neck, chest and abdomen CT showed no evidence of lymphoma.

A second chest CT performed 13 days later revealed peribronchovascular ground glass opacities of the mediobasal lower lobe segment of the left lung. Minimal tree-in-bud opacities in the left upper lobe led to testing for tuberculosis, but interferon- γ release assays were not suggestive of latent *Mycobacterium tuberculosis* infection.

Extensive autoantibody testing was negative for antinuclear antibody, antidouble-stranded DNA, extractable nuclear antigens subsets, cytoplasmic antineutrophil cytoplasmic antibodies and perinuclear antineutrophil cytoplasmic antibodies and borderline values for smooth muscle antibodies (1:80; reference range \leq 1:80).

Due to the patients persisting coughing, respiratory infections were repeatedly investigated. Oropharyngeal swab culture and *Streptococcus pneumoniae* urine antigen testing provided no further information, apart from the confirmation of oropharyngeal candida infection due to steroid therapy. Serologies for respiratory syncytial virus, coxsackievirus, echovirus, adenovirus, *Chlamydia pneumoniae*, *Legionella pneumophila* and *Mycoplasma pneumoniae* were negative. However, serologic assays were positive for pertussis toxin IgG (>200 U/mL; positive >100 U/mL) and IgA (>200 U/mL; positive >20 U/mL).

DIFFERENTIAL DIAGNOSIS

Since the cause of the patient's hospitalisation was severe, and because of the sustained development of facial swelling, the primary diagnostic investigation focused on ruling out possible causes for angioedema. At presentation, the patient's airway was unaffected and there was no immediate need for airway protection. The patient remained stable without signs of anaphylaxis and did not develop hives or other skin symptoms. Several allergies were listed by the patient, but despite the potential for an allergic disposition, which was also mirrored by elevated IgE levels, treatment with glucocorticoids did not show any effect and RAST testing was negative. The clinical symptoms as well as the treatment resistance to antihistamines and steroids made allergic, histamine-mediated angioedema unlikely.

There was no history of former episodes of angioedema, and no family members suffered from similar symptoms. On

review, the patient had never taken ACE-inhibitors, which ruled out ACE-inhibitor induced angioedema, and she also denied recent intake of nonsteroidal anti-inflammatory drugs or any new medications. Laboratory testing for complement factor C4 and C1-INH was added to rule out undiagnosed hereditary or acquired angioedema. Common causes of bradykinin-mediated angioedema therefore seemed equally unlikely.

We considered further differential diagnoses for facial swelling, such as hormonal dysfunctions. Normal thyroid function was not suggestive of myxoedema. Cortisol and ACTH levels were within the normal range and thus did not support Cushing's disease. Superior vena cava syndrome and right heart failure were also ruled out.

Since the white cell count with differential showed isolated lymphocytosis, and because lymphoproliferative disorders have been described as a possible cause of chronic urticaria, this was further investigated. However, no evidence of lymphoma or other malignancies were found.

Autoimmune disorders, such as Sjögren's syndrome, systemic lupus erythematosus, vasculitis and autoimmune thyroid disease have been found to be associated with chronic urticaria.⁶ However, the combination of the clinical presentation and complement factor and autoantibody testing were not suggestive of an underlying autoimmune disease.

Consequently, we had to reevaluate our diagnostic process and considered the rare case that exogen pathogens may be related to the development of angioedema. The only indication of an infection was given by the patients report of coughing for 6 weeks. Profound serological investigations were performed for respiratory infections and pertussis toxin assays were positive. The patient was not vaccinated during childhood. The 6-week history of coughing with bilateral subconjunctival haemorrhages and a syncope, lymphocytosis and the possibly infection-related ground glass formations found on the CT scan were in line with a recent *B. pertussis* infection. After a thorough elimination of differential diagnosis, our diagnostic pathway concluded in the final diagnosis of an infection with *B. pertussis*, and the rare case of infection-related angioedema.

TREATMENT

Oral antibiotic treatment with clarithromycin was prescribed (500 mg two times per day for 2 weeks) as an attempt at causal treatment. Macrolides are recommended as the standard treatment for *B. pertussis* infection, preferably during the early course.⁷ The dyspnoea, coughing and facial swelling gradually decreased during hospitalisation and consequently, the patient was able to be dismissed after 9 days.

OUTCOME AND FOLLOW-UP

Due to the gradually improving clinical status, the patient was dismissed and completed the course of oral antibiotic treatment at home. Six weeks later, a recovery was observed and the angioedema had receded completely.

DISCUSSION

The present case seems to be the first description of angioedema triggered by *B. pertussis* infection in an unvaccinated adult. Despite a thorough literature search, we could only find one case report of oedema in a newborn with *B. pertussis* infection.⁸

The diagnosis of *B. pertussis*-related angioedema was made according to current angioedema guidelines.⁹ This patient's angioedema can be classified as chronic spontaneous urticaria due to a duration of more than 6 weeks.¹⁰ Following the

established guidelines helped to rule out dangerous and common causes of angioedema.

Angioedema results from an increase in vascular permeability that causes a leak of fluid into surrounding tissues. In mast cell-mediated angioedema, inflammatory mediators such as histamine are released, leading to vasodilatation and fluid extravasation. In bradykinin-mediated angioedema (eg, ACE-inhibitor-induced angioedema or C1-esterase deficiency), similar pathophysiological mechanisms are assumed. Furthermore, bacterial, viral, fungal and parasitic infections have been found to be associated with chronic urticaria, although the exact pathomechanisms are unclear.¹⁰ According to our PubMed search ["*angioedema [ti] AND infect* [ti]*"], angioedema has been reported to be caused by different types of bacteria and viruses, most notably *Malassezia*, *C. pneumoniae*, *Parvovirus B19*, *M. pneumoniae*, *Trichinella*, *Blastocystis hominis*, *Helicobacter pylori*, *Giardia lamblia*, *Epstein-Barr virus* and *Echinococcus granulosus*.

B. pertussis develops its pathogenic effects via several toxins, which can be assumed to play a major role even in the development of angioedema. The most relevant toxin, Pertussis toxin, is a soluble exotoxin and is known to act systemically, leading to changes in G-protein mediated cellular responses.¹¹ It has also been shown to increase vascular permeability and thereby induce oedema.¹² Pertussis toxin results in vasodilatation by reducing the contractile properties of smooth muscle cells in resistance arteries, leading to oedema.¹³

Pertussis toxin is also responsible for lymphocytosis, which was another systemic response to *B. pertussis* infection seen in our patient. While neutrophilia is common in cases of bacterial infection, lymphocytosis is characteristic for *B. pertussis* infection and can even be used as a prognostic marker for poor outcomes.¹⁴

In adults, infection with *B. pertussis* is likely heavily underdiagnosed^{15 16} due to a few reasons. First, the clinical presentation may be atypical.¹⁷ Second, there has been increasing evidence to suggest that acellular vaccines introduced in the 1990s only last for 4–12 years, which leaves adolescents and adults at risk of

infection.^{2 18} For patients in the early disease stage, PCR is the diagnostic method of choice, after 3 weeks, serological diagnosis is recommended. PCR sensitivity is lower in adults compared with children.¹⁹ In our patient, 7–8 weeks after symptom onset, high titres of IgG and IgA antibodies to pertussis toxin were detected, which is highly sensitive and specific for a recent pertussis infection.^{17 20}

Antibiotic treatment effectively eliminates the bacteria and thereby reduces the risk of transmission. However, evidence suggests that it only affects the clinical course when given during the first week of infection.^{21–23} Even though the patient had been suffering from cough and angioedema for 7–8 weeks at the time of diagnosis, we still decided to prescribe antibiotic treatment due to the severity and duration of symptoms and the lack of other causal treatment options. It is possible that the clinical improvement was related to the initiation of antibiotic treatment, but may also represent the natural course of the disease with spontaneous improvement of symptoms.²⁴

To conclude, therapy-resistant angioedema and coughing for several weeks should prompt early testing for possible *B. pertussis* infection. In the clinical routine, the focus must be placed on achieving an early diagnosis and, above all, on disease prevention by vaccination.

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Patient's perspective

'I felt very much out of breath, as if something strangled me, and the first few days it only got worse. The coughing was also very hard to bear, as I was gasping for air after every coughing fit. After the course of antibiotics, I felt much better and the cough and feeling of suffocation were completely gone. Now, a year later, I still struggle with a raspy voice after the cortisone-induced thrush, but I lost 30 kg body weight a few weeks later, am working again and none of the symptoms returned.'

Learning points

- ▶ Vaccinated people may present with atypical symptoms of *Bordetella pertussis* infection, including angioedema.
- ▶ If a patient presents with angioedema, dangerous and common causes should be ruled out first, but uncommon causes such as *B. pertussis* infection should be considered.
- ▶ Pertussis toxin may be responsible for increased vascular permeability causing angioedema.
- ▶ Vaccination is most important for the prevention of pertussis transmission, especially in children <1 year who have the highest risk of mortality.

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