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Picibanil Therapy for Cervicofacial Lymphatic Malfomation

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Abstract We present the case of a 4-year-old boy who was born with a large cervicofacial lymphatic malformation. It was partially resected in the first year of life and treated with Picibanil/OK-432 injections at the age of three because of recurrence. Eight months later the boy developed a fulminant streptococcal toxic shock syndrome with cardiac arrest. After resuscitation, high dose intravenous antibiotic therapy and artificial ventilation for 2 weeks, he remained with an extensive hypoxic brain damage. As Picibanil/OK-432 is a preparation of lyophilized, low virulence group A *Streptococcus pyogenes* cells of human origin, the question of a causative relationship for the tragic outcome arises. We therefore report the clinical course and discuss the action and possible side effects of Picibanil/OK-432.

Key words Lymphatic malformation; OK-432; Picibanil; Streptococcal toxic shock syndrome

Introduction

Lymphatic malformations represent circumscribed or generalised congenital lesions of the lymphatic system, which are characterised by ectatic vessels. They are mostly detected at birth and become symptomatic during the first years of life in 80% of the affected children. In contrast to haemangiomas, they do not proliferate, but grow proportionately with the infant throughout the course of the individual's life.[1]

As the head and neck area represents the most common site for lymphatic malformations, these dysplasias may cause cosmetic impairment and may also interfere with breathing and swallowing. A trivial cold or infection, trauma or puberty can induce dramatic size progression resulting in life threatening complications.[2] As soon as the patient becomes symptomatic or as soon as any kind of complication start to emerge, some kind of treatment must be performed. The most widely accepted option is surgical excision of the lesion. But difficulties may arise, as lymphatic malformations tend to infiltrate adjacent structures. Incomplete resections will lead to recurrences in up to 30% of operated patients. Intraoperative complications, such as arterial bleeding, facial or hypoglossal nerve injury or airway compromise requiring tracheostomies are observed in up to 70% of cases.[3]

Extensive research led to sclerotherapy as an alternative treatment option. Picibanil/OK-432, a powder of low virulence group A *Streptococcus pyogenes* of human origin, became the most important and best-known agent for this purpose during the last years. It is injected into the macrocystic spaces and produces sclerosis by inducing circumscribed inflammation.[4] Numerous clinical studies

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prove its' high effectiveness and safety in the first- and second-line treatment of macrocystic lymphatic malformations.

As no severe or permanent complications have been reported so far, we report the case of a 4-year old boy suffering from a congenital lymphatic malformation of the head and neck. Eight months after Picibanil/OK-432 injection he developed a streptococcal toxic shock syndrome (TSS) and suffers from hypoxic-ischaemic encephalopathy today. We describe the clinical course of this child and discuss the action and possible side effects of Picibanil/OK-432.

Case Report

From birth on, a 4-year-old boy suffered from a lymphatic malformation, which extended from the right supraclavicular to the right parotid region. During the first months of life the size of the macrocystic lesion dramatically increased. Therefore, a surgical size reduction was performed in 2002. During the first postoperative years the lymphatic malformation was asymptomatic and not visible. However, remnants were detectable in ultrasonography. Due to an airway infection another size progression resulted in July 2005. After aspiration of the cystic fluid, Picibanil/OK-432 (Chugai Pharmaceuticals, Tokyo, Japan) injection was chosen as the treatment option of choice. It was injected with a concentration of 0.1 mg/ 10 ml sodium chloride. A slight rise in temperature was observed postoperatively but vanished by antipyretic therapy. Size of the lymphatic malformation clearly decreased in the postoperative course and the patient was free of symptoms for approximately 8 months.

In March 2006, the boy developed steadily increasing temperatures, a widespread red rash and some dizziness and disorientation over the course of one evening. During the ride to the emergency department of the general hospital in Herdecke, Germany, the patient lost consciousness in his parents' car. At arrival he was tachyarrhythmic, bradypnoeic and heart action arrested. After cardiorespiratory resuscitation of approximately 35 minutes the cardiopulmonary situation stabilised and the patient was transferred to a nearby paediatric intensive care unit.

At a closer look, we found two necrotic areas in the right-sided pre- and retroauricular region, which measured 4 x 3 cm and 9 x 3 cm, respectively. The parents were not aware of these lesions, but reported well-being of their child during the past months. Routine laboratory blood tests revealed a distinct leucocytosis with lymphocytosis, elevated C-reactive protein levels and highly elevated kidney and liver parameters (creatinine, AST, ALT, γ-GT). Wound swab and blood culture found high concentrations of group A *Streptococcus pyogenes* (GAS) along with *Staphylococcus capitis*. Further subtyping of the GAS bacteria was not performed. The clinical course of the disease and the verification of GAS bacteria in blood culture resulted in streptococcal TSS (Table 1) as diagnosis. After antibiotic resistence testing, the initial intravenous antibiotic therapy of penicillin and clindamycin was changed to

Table 1 Streptococcal toxic shock syndrome: clinical case definition[17]

1. Isolation of group A β-haemolytic streptococci
   (a) from a normally sterile site (e.g. blood, cerebrospinal fluid, peritoneal fluid, tissue biopsy specimen)
   (b) from a nonsterile site (e.g. throat, sputum, vagina)

2. Clinical signs of severity
   (a) hypotension: systolic blood pressure <90 mm Hg in adults or lower than the fifth percentile for age in children
   And
   (b) two or more of the following signs:
   - renal impairment: creatinine level >177 μmol/L (≥2 mg/dL) for adults or two times or more the upper limit of normal for age
   - coagulopathy: platelet count <100 x 10^9/L (≤100 x 10^3/μL) or disseminated intravascular coagulation
   - hepatic involvement: ALT, AST, or total bilirubin levels two times or more the upper limit of normal for age
   - adult respiratory distress syndrome
   - a generalised erythematous macular rash that may desquamate
   - soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

An illness fulfilling criteria 1(a), 2(a), and 2(b) can be defined as a definite case. An illness fulfilling criteria 1(b), 2(a), and 2(b) can be defined as a probable case if no other cause for the illness is identified

intravenous vancomycin, clindamycin and imipenam. The clinical situation stabilised and blood parameters normalised. After unproblematic extubation two weeks later and successful withdrawal of catecholamine support, the patient was found to have hyperreflexia and spasticity of the lower extremities. Rehabilitation of the child is still in progress.

Discussion

Even today surgical excision of lymphatic malformations of the head and neck is the therapy of choice in many places of the world. In Europe however, alternative treatment options become more and more accepted, as surgery holds potential risks consisting of trauma to important structures like nerves or vessels, incomplete resection of the lymphatic cysts leading to recurrence or unaesthetic scars. Intralesional sclerotherapy represents the leading alternative, of which Picibanil/OK-432 is the best known substance with the fewest side effects.[2,4-7]

It displays its highest effectiveness in macrocystic lesions, which are characterised by 1 to 4 cysts of several centimeters in diameter.[5] Aspiration of the fluid and intralesional instillation of the substance turns out to be simple, as long as ultrasonography is used. Injections at the recommended doses will cause damage to the endothelial cell lining ultimately resulting in resorption of the fluid and consecutively in fibrosis and shrinkage of the cysts. In comparison to other sclerosing agents like ethanol or bleomycin OK-432 does not penetrate the cystic wall.[6] This prevents the development of perilesional fibrosis. As described by other authors, this characteristic clearly facilitates surgery of cystic remnants, if necessary.[7-9]

In the right clinical setting a modest local inflammation with a mild systemic temperature rise might follow the injection. This reaction is induced by neutrophils and monocytes migrating into the cyst together with a consecutive increase of several mediators like tumor necrosis factor or Interferon-γ.[10] These so-to-say wanted side effects can easily be treated with local or systemic antiinflammatory/antipyretic agents and usually regress after 1 to 2 days.

Severe side effects are, however, rare. These may involve swelling of the lesion, compressing key structures such as the trachea. In this context urgent tracheostomies for securing the airways are reported in two cases.[2,6] Injections into blood vessels must be avoided, as this would induce systemic immunomodulatory responses with sepsis-like, life-threatening reactions. Other potential risks include anaphylaxis to either the bacteria-derived protein or the penicillin contained within the preparation (used for bacterial breakdown).[11] That is why hypersensitivity to penicillin must be ruled out before treatment. This is often difficult, as children at the age of 1 or 2 often do not present any history of medication. These kinds of complications would all develop within a few hours after Picibanil injections. For reducing their risk we recommend the observation of patients for at least 24 hours after treatment. In contrast, late onset-complications evolving weeks or months after Picibanil treatment have not been reported at all.

Although Picibanil/OK-432 consists of lyophilized, low virulence Su strain group A *Streptococcus pyogenes* of human origin, streptococcal TSS 8 months after treatment is also unlikely to occur. The attenuated bacteria have lost their streptolysin S-producing ability during the production process.[12] This bacterial pathogen is known to be the main factor in the pathogenesis of streptococcal TSS, as it is responsible for osmotic lysis of tissue culture cells and a variety of host's cells, including leukocytes and platelets.[13] However, other streptococcal pathogens like pyrogenic exotoxins, nucleases and extracellular products such as streptolysin O remain after the industrial attenuation of the bacteria, but only induce mild immunomodulatory responses.[10] Furthermore, some authors report excision of nodular remnants after full response to Picibanil therapy. Histology revealed endothelial cell death and fibrous tissue without any sign of persisting bacteria in these cases.[5]

Consequentially, the streptococcal TSS 8 months after Picibanil treatment occurred independently in the reported case. As generally known, the child's own flora of *Streptococcus pyogenes* seems to be responsible for the septic infection. Some patients with lymphatic malformations experience recurrent local infections, as well as severe systemic infections.[14] This explains the presence of necrotic skin, which has to be accounted as the site of bacterial entry. The septic shock may also be related to recent findings, that patients with large bilateral lymphatic malformations often have low numbers of circulating lymphocytes.[15,16] In cases of infection, the risk of an overshooting bacterial dissemination is higher due to the reduced immunomodulatory response. This is proven by the fact, that patients with lymphatic malformations associated with lymphocytopenia were hospitalised more frequently than patients without lymphocytopenia and had increased antibiotic use.[15,16] However, the aetiology of lymphocytopenia in patients with lymphatic malformations is unclear, although there is strong association to advanced stage and structure.[15]

Conclusion

Injections of Picibanil/OK-432 represent a serious option in the therapy of macrocystic lymphatic malformations of the head and neck and should always be considered in the first line-treatment. In comparison to surgical excision they only cause mild side effects of short duration. Severe complications are very rare and mainly concern airway compromise due to sudden size progression. A relationship to late onset streptococcal toxic shock syndrome cannot be established. However, thorough diagnostics prior to Picibanil/OK-432 injections are absolutely necessary, which also include the characterisation of the patient's immunomodulatory status.

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