Case Report

Chronic mastoiditis associated with leukocyte adhesion deficiency type 1: A case report

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ABSTRACT

Adhesion molecules work for leukocytes to infiltrate to the site of inflammation. Deficiencies of these molecules can disturb neutrophil migration and thus inflammation. This group of illnesses is named leukocyte adhesion deficiency (LAD) syndromes. Mastoiditis is a very rare and unexpected complication. CD 18 count is the prognostic factor and might affect the treatment modalities. We report the case of a six-year-old girl with LAD type 1 who presented with chronic mastoiditis and the treatment of this unusual presentation.

Keywords: Chronic middle ear disease; leukocyte adhesion deficiency; pediatric ear disorders; pediatric mastoiditis; primary immunodeficiency syndromes.

Adhesion molecules located at the endothelia and cell membranes are important mediators for leukocyte migration and adhesion to vascular endothelia at the site of inflammation.[1,2] Margination, rolling, adhesion and migration are the main steps necessary for leukocytic infiltration to inflammatory tissue, and are dependent on fully functional adhesion molecules.[3] Deficiencies of these molecules result in inadequate neutrophil migration and inflammatory response, termed leukocyte adhesion deficiency (LAD), and these diseases are classified as primary immunodeficiency syndromes.

There are three types of leukocyte deficiencies: type 1 LAD is caused by lack of β2 integrin/CD18 at the leukocyte membrane.[1,2,4-7] Type 2 LAD involves a defect in E and P selectin ligands. Type 3 LAD is caused by insufficient activation of β2 integrins, and clinically is similar to LAD type 1.[8]

Leukocyte adhesion deficiency type 1, which is inherited in an autosomal recessive manner, is characterized by delayed separation of the umbilical cord, omphalitis, recurrent periodonditis and gingivitis, pyogenic bacterial infections (chronic otitis media, pneumonia, peritonitis, cellulitis), necrosis and ulcerations of the skin.[3]

With informed consent obtained from her parents, we report the case of a six-year-old girl with LAD type 1 who presented with chronic mastoiditis and the treatment of this unusual presentation.

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CASE REPORT

A six-year-old girl with a definitive diagnosis of LAD type 1 presented with multiple skin ulcers and was interned to the pediatrics service. The patient was lost to follow-up for one year. Her general condition was poor and her skin was pale. There were multiple necrotic dry skin lesions on the trunk, abdomen, left anterior thigh and retroauricular region (Figure 1). Empiric antibiotic treatment was started by a pediatric immunologist.

The patient was referred to our department for the foul smelling right retroauricular skin lesion. At the retroauricular region a necrotic skin lesion and a fistulous orifice on the skin were present (Figure 2). On the otomicroscopic examination, minimal scar tissues on the external ear canal and granulation tissues on the tympanic membrane were observed. High resolution temporal bone computed tomography revealed soft tissue images filling the mastoid cavity, mastoid apex and middle ear (Figure 3).

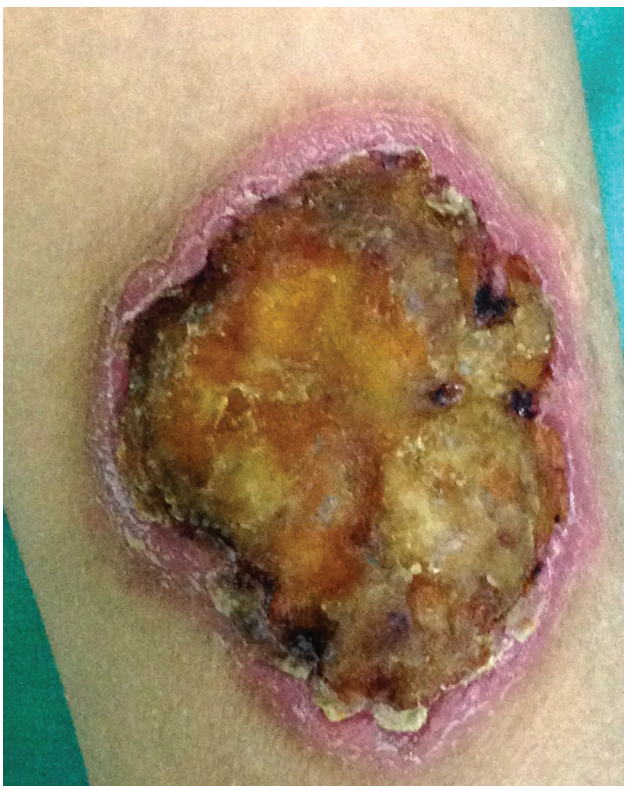

Figure 1. *Necrotic dry skin lesion on the left anterior thigh.*

A cortical mastoidectomy was performed under general anesthesia. Necrotic tissues and granulation tissues in the external ear canal and over the tympanic membrane were debrided. Although the mastoid cavity was filled with granulation tissue no cholesteatoma or epithelium was observed. There was no granulation tissue observed in the tympanic cavity and epitympanum. Ossicular movements were not disturbed. The margin of the fistula orifice was

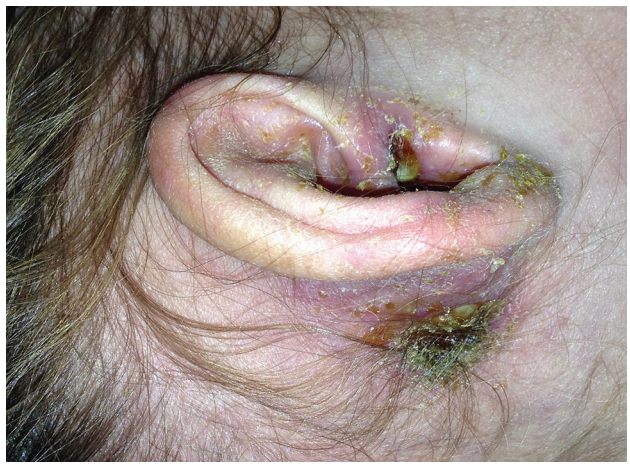

Figure 2. *Necrotic skin lesion and a fistulous orifice in the right retroauricular skin.*

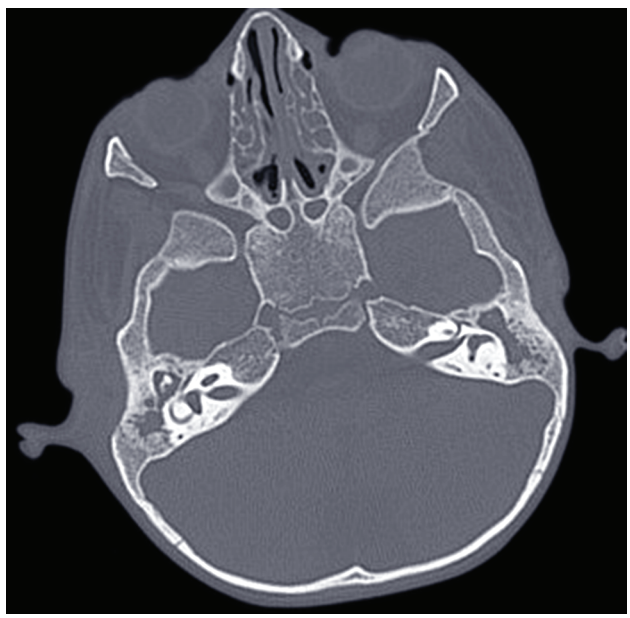

Figure 3. *Temporal high-resolution computed tomography showing soft tissue images in the antrum and epitympanum bilaterally.*

resected and the defect was sutured primarily. Wound care was done daily, and the ear packs were taken out at the first postoperative week. On her fourth year follow-up, no skin and otoscopic pathologies were observed.

DISCUSSION

Adhesion molecules have a vital role in leukocyte-endothelium interaction during inflammation, such as chemotaxis, adhesion, rolling and transmigration. Defects and deficiencies in these molecules result in various clinical syndromes classified as leukocyte adhesion defects.[1,2] There are three types of leucocyte deficiencies: type 1 deficiency is caused by lack of β2 integrin/CD18 at the leukocyte membrane. A mutation of the gene at the long arm of chromosome 21 (21q22.3) which is responsible for synthesis of the CD18 molecule of the β2 integrin family is responsible for this disease, and this disease is characterized by lack of CD18 molecules at the leukocyte membrane.[1,2,4-7] In leukocyte adhesion defect type 2, there is a defect in E and P selectin ligands, and thus adhesion and rolling of the leukocytes to the endothelia cannot be achieved. Type 3 LAD is caused by insufficient activation of β2 integrins and clinically similar to LAD type 1.[8]

In LAD type 1, which was first described by Hayward in 1979, adhesion and transmigration phases of the adhesion cascade cannot be performed. The incidence of this disease is not well known.[3,9] The disease mainly affects the skin and mucosa, and may result in fatal bacterial infections. Due to the lack of inflammation, necrotic lesions develop, and wound healing is delayed. First findings are delayed separation of the umbilical cord and omphalitis.[3,9] There is no increased proclivity to viral infections, but an increase in infections with *Staphylococcus aureus*, gram (-) enteric microorganism and fungi can be seen. Recurrent otitis media, perirectal abscess, cellulitis, chronic periodontitis are other commonly seen infections.[3,9] *Pseudomonas Aureginosa* and *Escherichia Coli*, which are gram (-) microorganisms, were cultured from the infected tissue excised during surgery. On histopathologic examination, neutrophils are not observed in the tissue samples that are taken from the infected field. The severity of the complications is directly proportional to the degree of CD18 deficiency. In patients with CD18 count lower than 1% of the normal value, the disease presents early and severely. If the CD18 count is between 2.5-30% of the normal value, mild clinical symptoms can be seen. The immunological assessment of our patient showed the ratio of CD11a/CD18 was 82%, CD11b/CD18 was 8% and CD11c/CD18 was 15%.

Consistent with the literature, our patient presented with chronic skin and mucosal ulcerations. Although recurrent otitis media is a known finding of this disease, chronic mastoiditis is a very rare complication. In 1992 Voss and Rhodes[10] was one of the first physicians to report the relation between LAD and recurrent otitis media. An infant with recurrent otitis media and tympanic membrane perforation and a history of delayed umbilical cord separation was presented in her paper. Mastoiditis or other otolojic complications were not present.[10] Martinez et al.[11] reported the case of a five-month-old boy with bilateral coalescent mastoiditis and sigmoid sinus thrombosis as a complication of LAD. Compared to these two cases, our patient did not have tympanic membrane perforation and otorrhea. Instead, our patient had a retroauricular necrotic skin lesion and granulation and necrotic tissue in the external ear canal. Both of the authors treated their patients with broad-spectrum antibiotics as was done in our case. In line with our approach, Martinez reported that cortical mastoidectomy was performed for coalescent mastoiditis.

Leukocyte count of these patients can differ between 20.000 to up to 1.000.000 with a predomination of granulocytes.[12] The leukocyte count of our patient was 38.700. Loss of neutrophil mobilization can be determined by *in vivo* Rebuck skin window test.[1] Chemotaxis is severely damaged *in vitro*.[12] Also, defects in β2 (CD18) subunit of integrin molecules can be shown by using monoclonal antibodies in flow cytometry. Definite genetic diagnosis can be done by using sequence analysis.[9,12]

Treatment for mild diseases is heavy antibiotic treatment and supportive care during acute infections. Prophylactic antibiotic use can decrease the risk of infection. Also, granulocyte

transfusions can be effective during infections. In severe cases, definite treatment is bone marrow transplantation.[12] In our case, debridement of the infected soft tissues was needed for treatment because antibiotic treatment alone was not sufficient.

In conclusion, leukocyte adhesion defect type 1 must be considered for patients with recurrent soft tissue infections with high leukocyte counts. Defects in β2 (CD18) subunit of integrin molecules can be shown by using monoclonal antibodies in flow cytometry. Antibiotic therapy and supportive care should be provided for active infections and the definite treatment is bone marrow transplantation. The otorhinolaryngologist should keep in mind LAD type 1 in children with otherwise unexplained intractable chronic otitis media and even mastoiditis as in our case.

Declaration of conflicting interests

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