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A case of a 4-year-old boy with difficult-to-diagnose skin infection with nontuberculous mycobacteria

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Abstract

Nontuberculous mycobacteria infections have become increasingly common in recent years and have even been confirmed in children. In addition to other organs, they can even affect the skin; nevertheless, in children lymphadenitis is the most common manifestation of the infection. The diagnosis of mycobacterial skin infection is based on patient history, clinical picture, histopathological changes, and tuberculin test result. Evidence of the causative agent in the lesion is confirmed with cultivation and PCR, two of the main tests that help determine the type of the causative mycobacteria. Here we report the case of a 4-year-old boy that presented with a few pink-to-livid papules and one plaque with a central crust on the skin of the left knee and an enlarged popliteal lymph node, highly suspicious of nontuberculous mycobacteria infection. Among the laboratory results, only a positive QuantiFERON and Mantoux test stood out. In addition, in the histopathological report, superficial and deep inflammatory elements were described, which could be due to an infection with nontuberculous mycobacteria. Despite negative cultivation and PCR, in agreement with a pediatric pulmonologist we decided to introduce antibiotic therapy for 6 months. Treatment was successful, we achieved regression of the skin lesions, and lymphadenitis was no longer present.

Keywords: nontuberculous mycobacteria, children, QuantiFERON test, lymphadenitis

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Introduction

Infection with nontuberculous mycobacteria is considered an infection caused by mycobacteria other than *Mycobacterium tuberculosis* or *M. leprae*. In recent decades, infections with nontuberculous mycobacteria have been becoming more common, and they can also be seen in children. They can cause pulmonary, lymphatic, dermatological, skeletal, genital, and urological diseases, but in children, the infection mostly manifests as lymphadenitis (1). The diagnosis of mycobacterial infection is based on the patient history, clinical picture, histopathological changes, and tuberculin and QuantiFERON test results. In the case of nontuberculous mycobacteria, because of slow growth in the culture, the PCR method for identification of the microorganism is commonly used (2).

Case report

We report the case of a 4-year-old boy that was referred to our outpatient clinic due to wart-like lesions on his left knee. The first lesion was observed a few months before the examination, and it did not itch or hurt. A month before the examination, the lesion had enlarged and new ones had appeared around it; the boy's mother described them as purulent bumps.

Except for problems with recurrent toenail inflammation since birth, the patient was otherwise healthy. The family history was negative for skin diseases, and no one in the family had noticed similar changes on the skin. In the recent past, he had had no contact with aquariums or aquatic organisms that could lead to infection.

On examination, a few pink to livid papules were visible on the left knee and one plaque with a central crust in the middle (Fig. 1). Medially on the left knee, a firmer subcutaneous resistance measuring approximately 2 × 1 cm was palpated, suspicious for an enlarged lymph node.

In the differential diagnostics, we initially considered molluscum contagiosum infection with surrounding eczema and impetiginization, herpes simplex virus (HSV) infection, or deep mycosis.

Due to the unclear clinical picture, additional diagnostics were performed. The full blood tests were within normal ranges, except for mild lymphocytosis (3.42 10^9/l, 56.8%). A native mycological examination of the lesion on the left knee was performed, and the sample was sent for cultivation; swabs for HSV and varicella-zoster virus (VZV), serology for *Toxocara canis* and *Leishmania* spp., and a pustule swab for pathogenic bacteria were performed. Tissue biopsy, additional PCR examinations for *Leishmania* spp., and cultivation and PCR testing of the skin for nontuberculous mycobacteria were performed. The results of all the tests performed were negative, and therefore we were able to rule out HSV infection and deep mycosis.

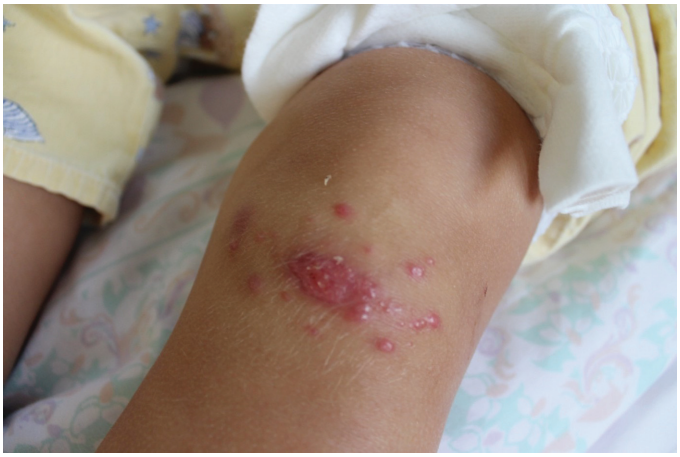

Figure 1 | Presentation at the beginning of diagnostics, in March 2019.

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Because of a positive QuantiFERON test we performed a chest X-ray, in which thickened walls of the central bronchi were visible combined with peribronchovascular infiltrates. After consultation with a pulmonologist, a throat swab was performed to exclude *Mycoplasma pneumoniae* and respiratory viruses, and the results were again negative.

An ultrasound report of the left knee described two hypoechoic changes on the medial side of the knee, where subcutaneous resistance was palpated and changes appeared as reactive lymph nodes.

The histopathological report described superficial and deep granuloma inflammation; in some granulomas, there were individual neutrophilic granulocytes without convincing necrosis, which could be due to an infection with nontuberculous mycobacteria. Leishmaniasis was histologically unlikely. Additional staining (Grocott, Ziehl–Neelsen Fite, and auramine–rhodamine stain) did not identify the presence of nontuberculous mycobacteria or fungal elements.

After receiving all the results, following an unclear diagnosis, the patient was hospitalized for a second time for another biopsy, cultivation, and PCR for nontuberculous mycobacteria because infection with nontuberculous mycobacteria was now the main diagnosis based on the clinical picture. The results were again negative; however, upon admission, the patient underwent a tuberculin test, and the result was positive (15 mm).

Based on the clinical picture, which was very suspicious for infection with nontuberculous mycobacteria and a positive QuantiFERON and Mantoux test, the patient was examined by a pediatric pulmonologist. Because tuberculosis was ruled out, we decided to treat the patient as being infected with nontuberculous mycobacteria. In May 2019, the patient was started on treatment with a combination of antibiotic therapy based on the guidelines, with azithromycin and trimethoprim/sulfamethoxazole for an estimated time of 6 months. No additional local treatment was administered.

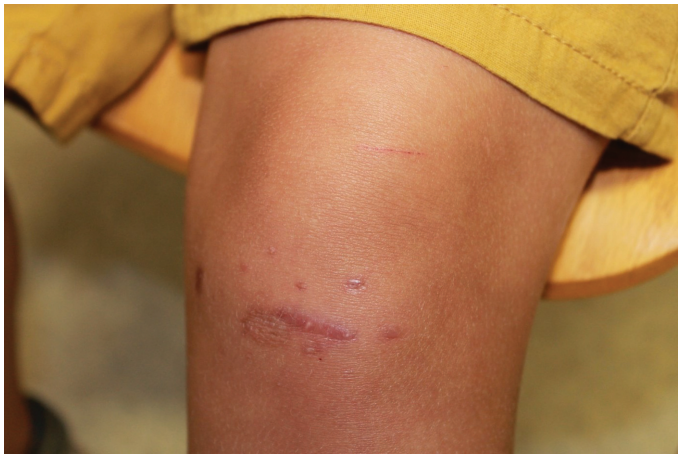

Figure 2 | After 3 months of treatment with two-course systemic antibiotic therapy, in August 2019.

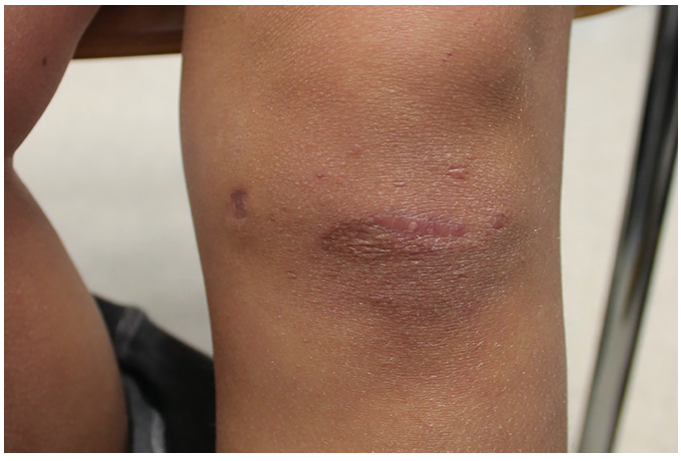

Figure 3 | At the end of October 2019, after 6 months of systemic antibiotic therapy, treatment was completed.

During the patient's treatment with systemic antibiotic, he was regularly monitored and gradual regression of skin changes was noted (Fig. 2). At the end of October 2019, after 6 months of systemic antibiotic therapy, treatment was completed. A scar after the biopsy was visible on the left knee, but there were no fresh papules, pustules, or inflammation (Fig. 3). The enlarged lymph node was no longer palpable. We continued to advise avoiding aquariums, aquatic organisms, and moist soil because they could be a possible source of infection. He was also re-examined by a pulmonologist, who did not notice any changes in the chest X-ray and clinical examination of the boy.

Discussion

Infections with nontuberculous mycobacteria are caused by mycobacteria other than *M. tuberculosis* or *M. leprae*. Over the past decades, infections with nontuberculous mycobacteria have been on the rise, especially in people with immune deficiencies (1). Risk factors for infection include immune deficiency or immunosuppression (HIV), chronic pulmonary diseases (chronic obstructive pulmonary disease), bronchiectasis, cystic fibrosis, diabetes, hematological cancers, intravenous drug use, tattoos, and exposure to aquatic organisms (3).

Nontuberculous mycobacteria can be found in moist soil, house dust, water, dairy products, cold-blooded animals, plants, and even human excrement (1, 4, 5). They are the most common bacteria on the surface of showerheads (6). Transmission can be caused by inhalation, ingestion, or through the skin, causing dermatological, pulmonary, lymphatic, skeletal, genital, and urological diseases (1).

Nontuberculous mycobacteria are classified into several different groups based on the possibility of pigment production and growth rate (slow or fast growth) (1, 3). Infections of the skin and soft tissues are mainly caused by fast-growing mycobacteria. *Mycobacterium fortuitum*, *M. abscessus*, and *M. chelonae* are considered fast-growing mycobacteria, whereas *M. marinum*, *M. ulcerans*, *M. kansasii*, and *M. haemophilum* are considered slow-growing mycobacteria (7).

Clinically, in children infection most commonly manifests as lymphadenitis, but it may also appear as skin and soft tissue infection, lung involvement, or disseminated infection (4, 8). Despite the fact that many children are exposed to nontuberculous mycobacteria on a daily basis, symptomatic infections are rare (6). In immunocompetent individuals, skin infection usually follows skin trauma, which serves as an entrance for later localized infection. In contrast, immunocompromised patients typically lack a history of trauma, multiple lesions follow hematogenous spread without a suspected entry point, and involvement of other organs is also more common (5). Nontuberculous mycobacteria should be considered in infections following injury, surgery, or cosmetic procedures when there is no response to the standard antibiotic treatment regimen (7).

Development of the infection depends on several factors, including type of bacteria, level of exposure, and the immune sta-

tus of the host (1). Infection with nontuberculous mycobacteria is generally manifested as a respiratory tract infection, most commonly caused by *M. avium-intracellulare* complex (MAC). As already mentioned, lymphatic disease is more common in children than in adults, and the most common cause is MAC (3).

Infection of the skin and soft tissues typically presents as solitary or multiple nodules in linear distribution, following local vessels or lymphatic ducts. Local lymph nodes are usually involved. The clinical picture often appears as nonspecific inflammatory changes or plaques. Deeper-lying structures can also be affected (e.g., sinuses) (7). Fish tank granuloma caused by *M. marinum* is a characteristic skin manifestation. As the name suggests, there is a connection with an aquatic environment. In a warmer, tropical environment, *M. ulcerans* causes Buruli ulcer, which most often causes changes on the lower extremities (3, 5). Deep fungal infection presents with a similar clinical picture, and in such patients it is the main differential diagnostic option. Disseminated infection occurs extremely rarely; MAC is again the most common causative agent, and the same is true for gastrointestinal infection. Musculoskeletal infection is not a typical presentation and can potentially be caused by all nontuberculous mycobacteria (3).

Diagnosis of infection with mycobacteria is based on the patient history, clinical picture, histopathological changes, tuberculin test result, and evidence of the causative agent in the lesion (2).

The Mantoux skin test was developed by Koch in 1890, and in 1912 the intradermal technique currently used today was further developed by Charles Mantoux, a French physician. The most commonly used tuberculin is a purified protein derivative from *M. tuberculosis* culture. A standard dose of 5 tuberculin units (TU) (0.1 ml) is injected intradermally, and the result is read after 48 to 72 hours. Erythema is not included in the measurement. A positive result depends on the associated risk factors. A result > 15 mm is positive in children without associated risk factors, whereas in children with risk factors the positive result is set at lower values (9). Nontuberculous mycobacterial infections are usually associated with an induration of 3 to 15 mm on the standard tuberculin test (10).

The QuantiFERON test, which measures the amount of interferon released in the blood, can also be used in the diagnosis (2). A major limitation of the tuberculin skin test is false-positive results in people that received the BCG vaccine, whereas a blood test is more specific in BCG-vaccinated people. Blood tests such as the QuantiFERON test use early secretory antigen target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10) as tuberculosis-specific antigens to elicit a T-cell response, and they were chosen because they are absent from the BCG vaccine (11). Nontuberculous mycobacteria possess some *M. tuberculosis*–specific antigens, which may result in a positive QuantiFERON test (12).

Nontuberculous mycobacteria grow extremely slowly in culture. Therefore, instead of a culture, the PCR method, which is specific and sensitive, is commonly used (2).

Antimicrobial resistance is common in nontuberculous mycobacteria and often develops during antibiotic therapy. Therefore, treatment consists of a combination of antibiotics normally based on macrolides (7). Only long-term treatment with a combination of different groups of antibiotics (macrolides, clarithromycin, and azithromycin) can lead to a definitive cure. Other treatment options include rifabutin, ethambutol, isoniazid, aminoglycosides (amikacin or streptomycin), fluoroquinolones (moxifloxacin), cefoxitin, and para-aminosalicylate (3).

Conclusions

We would like to emphasize that the cutaneous lesions seen in our patient were clinically highly suspicious for infection with nontuberculous mycobacteria. Although we were not able to confirm diagnosis with a histopathological exam, cultivation of tissue, and PCR test, in our case a positive QuantiFERON and Mantoux test led to the decision about the possible cause and the treatment. Those two positive results, along with the exclusion of tuberculosis, helped us determine the choice and length of treatment. Treatment based on the guidelines for nontuberculous mycobacteria led to clinical improvement of the cutaneous lesions and lymph node enlargement.

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