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Case Report

Diphtheria-like illness disguised as Kawasaki disease: Case report

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ABSTRACT

Introduction: Diseases caused by *Corynebacterium* spp. are rare in humans. The atypical clinical presentation of the infection may cause diagnostic difficulties.

Aim: In this case report, we present the medical history of a 3-year-old patient admitted to the hospital with symptoms characteristic of Kawasaki disease.

Case study: The child presented with a persistent fever, a red throat, conjunctival hyperaemia, enlargement of the submandibular and cervical nodes, maculopapular rash on the trunk. In the laboratory tests the significant elevation of inflammatory markers, an increased plasma concentration of N-terminal pro B-type natriuretic peptide (NT-proBNP) were observed. Additionally, the girl was not fully vaccinated. Despite the administration of antibiotic therapy, the patient's general condition deteriorated. Irregularities in heart rhythm were also noticed. For these reasons, the patient was transferred to a tertiary reference hospital. Although the criteria for Kawasaki disease were met, due to the persistent coating on both tonsils and pharynx, further diagnostics were deemed necessary. A microbiological examination revealed the cultivation of coryneform bacteria. Appropriate antibiotic treatment led to the improvement of the girl's condition.

Results and discussion: The described case indicates two important pediatric problems. The first one concerns the diagnosis of fevers with atypical symptoms related to rare infections. The second one concerns the similarity of symptoms of infections and Kawasaki disease.

Conclusions: Attention should be paid to the atypical course of infection, which may mimic other diseases. In the differential diagnosis, it is worth considering opportunistic infections, rare microorganisms.

1. INTRODUCTION

The human upper respiratory tract consists of microbial communities, among which *Corynebacterium* spp. are found as a component of the nasopharyngeal mucosa's commensal flora.^{1,2} *Corynebacterium* spp. may influence the condition of the immune system. There is a correlation between the presence of these microorganisms in the flora of the throat and increased resistance to viral and bacterial infections in the respiratory system.^{3–5} In some cases, they may constitute an important infectious agent.^{6,7} These aerobic, Gram-positive bacilli can cause diphtheria-like illness, especially in immunocompromised patients.⁷

Kawasaki disease (KD) is an acute, systemic vasculitis of unknown etiology, most commonly occurring in children under 5 years of age. The diagnosis of KD should be considered in any child with a febrile illness and the presence of inflammation, particularly if it persists longer than 4–5 days. If left undiagnosed and untreated, 25%–30% of patients develop coronary artery abnormalities. § The clinical symptoms may be similar to acute infection. The role of infection in the pathogenesis of KD is widely discussed, but viral rather than bacterial infections are emphasized. 11

2. AIM

The main purpose of this article is to draw attention to the atypical course of bacterial infection, which may mimic other disease syndromes. Such infections should be considered in the differential diagnosis, which will help avoid exposing the patient to complications or ineffective treatment.

3. CASE STUDY

A 3-year-old girl was admitted to the hospital in a moderate state, presenting with a fever (5th day) and weakness. On physical examination a fine, spotted rash was visible on the chest, the skin was sweating, small scars after varicella were visible, swollen asymmetric (right larger than left) tonsils, white coating on the right tonsil, the posterior pharyngeal wall was red, the lymph nodes in the submandibular and cervical regions enlarged, more on the right side and maculopapular rash on the trunk. Auscultation revealed normal vesicular breath sounds and regular heart rate, with no evident murmurs. Capillary refill less than 2 s, soft abdomen, non-tender on palpation, visceral organs: liver not enlarged, palpable spleen 1 cm below the left costal margin.

The child had a history of Multisystem Inflammatory Syndrome in Children (MIS-C) following a SARS-CoV-2 infection. During that episode, arrhythmia was diagnosed. After the discharge, she was under the care of a cardiologist due to mitral valve insufficiency and persistent premature ventricular contractions. The child was not fully vaccinated due to the mother's negative attitude towards the procedure. Upon medical evaluation, it was reported that the child had multiple recurrent upper respiratory tract infections. She was treated by a dermatologist due to genital warts (mom also had genital warts during pregnancy). One month prior her current hospitalization, she had chickenpox.

On the current admission day, laboratory tests revealed elevated inflammatory markers, increased N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, and anemia (Table 1). Initial management with a third-generation cephalosporin did not yield improvement, prompting referral to a higher-level facility.

Table 1. Hematological indices and inflammatory biomarkers assessed during patient's hospitalization.

Y7	Day of hospitalization							D.C.
Variable	1	2	3	4	5	6	7	Reference range
WBC, \times 10 $^3/\mu$ L	13.10↑	15.40↑	8.30	17.11↑	16.41↑	16.26↑	8.06	4.00-12.00
RBC, \times 10 ⁶ / μ L	4.14	3.84	3.45	3.54	2.78↓	3.27	3.44	3.10-5.30
HGB, g/dL	11.2↓	10.2↓	9.2↓	9.2↓	7.2↓	8.3↓	8.7↓	11.8–14.7
PLT, $ imes 10^3/\mu ext{L}$	239	219	200	232	358	476↑	683↑	140-410
NEU, $ imes 10^3/\mu L$	7.53	10.21↑	4.42	11.17↑	11.47↑	12.13↑	3.77	1.50-7.00
LYM, $ imes 10^3/\mu L$	4.07	3.29	2.69	3.71	3.14	2.63	3.48	1.50-7.00
MONO, \times 10 $^3/\mu$ L	1.29↑	1.57↑	1.07	2.10↑	1.70↑	1.30	0.53	0.20-1.20
EOS, $ imes 10^3/\mu L$	0.11	0.14	0.06	0.01	0.03	0.11	0.23	0.00-0.60
BASO, \times 10 $^{3}/\mu$ L	0.14	0.17	0.07	0.12	0.07	0.09	0.05	0-0.15
CRP, mg/L	189.3↑	235.9↑	245.0↑	298.9↑	251.7↑	_	99.2↑	0-0.5
PCT, ng/mL	1.29↑	2.97↑	2.75↑	2.51↑	1.32↑	-	_	< 0.50
ESR, mm/h	_	_	-	60↑	54↑	-	_	2–15
NT-proBNP, pg/mL	11470↑	_	1569↑	_	_	320↑	_	0–83

Comments: WBC — white blood cells; RBC — red blood cells; HGB — haemoglobin; PLT — platelet, NEU — neutrophils; LYM — lymphocytes; MONO — monocytes; EOS — eosinophils; BASO — basophils; CRP — C-reactive protein; PCT — procalcitonin; ESR — erythrocyte sedimentation rate; NT-proBNP — N-terminal pro B-type natriuretic peptide.

Table 2. Patient's symptoms in relation to KD diagnostic criteria.

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KD diagnostic ^{8,9}	Definition ^{8,9}	Patient's symptoms					
Fever	Duration of 5 days or more	More than 5 days					
And a minimum 4 out of 5 criteria							
Conjunctivitis	Bilateral, bulbar, conjunctival injection without exudate	Bulbar conjunctivitis					
Lymphadenopathy	Cervical, often >1.5 cm usually unilateral	Cervical >1.5 cm; bi- lateral					
Rash Maculopapular	Diffuse erythroderma or erythema multiforme	Maculopapular rash on the trunk					
Changes of lips or oral mucosa	Red cracked lips, strawberry tongue or diffuse erythema of oropharynx	Diffuse erythema of oropharynx; swollen asymmetric (right larger than left) tonsils, white coating on the right tonsil					
Changes to extremities	Erythema and oedema of palms and soles in the acute phase and periungual desquama- tion in subacute phase	Absent					

Table 3. Patient's symptoms in relation to the incomplete KD diagnostic criteria.

KD diagnostic ^{8,9}	Definition ^{8,9}	Patient's symptoms					
Fever	≥5 days	≥5 days					
CRP, mg/L	30.0	251.7					
ESR, mm/h	40	54					
Need at least 3 laboratory findings							
Platelets	\geq 450 $ imes$ 109/L after day 7th of fever	$683 \times 10^9 / L (day 7^{th})$					
Albumin, g/L	30	39.3					
ALT, U/L	>39	10					
WCC	\geq 15 × 10 $^{9}/L$	$16.41\times10^9\!/L(day5^{th})$					
Urine, WCC/hpf	≥10	3–5					
Echocardiogram	abnormal	normal					

Comments: ALT – alanine transaminase; hpf – high power field; WCC – white cell count; ESR – erythrocyte sedimentation rate.

Persistent fever and other symptoms (Table 2), as well as diagnostic tests (Table 3) for incomplete KD are presented below. The patient met the established criteria for the initially suspected pathology. Nevertheless, a differential diagnosis was performed.

There were significant abnormalities in the blood test results. Inflammatory markers demonstrated an elevated C-reactive protein at 298.9 mg/L, the erythrocyte sedimentation rate reached 60 mm/h, interleukin-6 level at 180 pg/mL (normal range: 1–7 pg/mL), an increased platelet count, procalcitonin was elevated at 2.05 ng/mL, all exceeding their respective normal ranges. The patient exhibited leukocytosis with neutrophilia (Table 1). The treatment with cefotaxime was continued alongside the addition of vancomycin. Follow-





Figure 1. The photograph depicts changes observed during a physical examination. A whitish exudate was present on the posterior pharyngeal wall and on both tonsils.

ing a laryngological consultation, an infection with anaerobic bacteria or Plaut-Vincent's angina was suspected, vancomycin was replaced with metronidazole. Examination of the oropharynx revealed a grayish-white membrane on the tonsil and posterior pharyngeal wall (Figure 1). During a swab collection for microbiological examination, the membrane detached with slight bleeding. Based on the patient's general clinical condition the decision was made to administer clindamycin instead of metronidazole. Further tests conducted on the smear from tonsils in the microbiology laboratory identified a coryneform, gram-positive, aerobic bacillus, raising suspicion of C. diphtheriae infection. Further examination using real-time polymerase chain reaction (PCR) method ruled out infections with C. diphtheriae, C. ulcerans and C. pseudotuberculosis. The patient's clinical condition progressively improved over the following days, leading to discharge (Figure 2). The basic immunological tests were performed 5 months later. Panel for extended immunophenotyping of lymphocyte subpopulations with dihydrorhodamine (DHR) flow cytometric analysis was carried out. The IgG subclasses were within the normal range. The results did not indicate primary immunodeficiency.



Figure 2. The photograph depicts the condition of the girl after antibiotic therapy. The posterior pharyngeal wall and both tonsils showed no exudate.

5. DISCUSSION

The report describes the medical history of a pediatric patient presenting with a diphtheria-like illness. Detailed diagnostic tests identified an infection of Coryneform bacteria, specifically excluding *Corynebacterium diphtheriae*, *C. ulcerans*, and *C. pseudotuberculosis*. The administration of a treatment regimen consisting cefotaxime and clindamycin improved the patient's general condition. The patient's incomplete vaccination history may have contributed to the disease.

Diseases caused by *Corynebacterium* species are exceedingly rare, with an increasing number of infections noted in recent years. ¹² The implementation of protective vaccination programs has led to a significant reduction in infections caused by the *C. diphtheriae*. ¹³ These pathogens can cause various infections, including respiratory tract infections such as pharyngitis, ¹⁴ necrotizing tracheitis ¹⁵ and pneumonia. ¹⁶ *Corynebacterium pseudodiphtheriticum* has also been associated with endocarditis, ¹⁷ keratitis, ¹⁸ septic arthritis ¹⁹ and urinary tract infections. ²⁰ These diseases have largely been reported in immunosuppressed patients. ¹⁴⁻¹⁷

The atypical presentation of this infection, diagnostic difficulties and high resistance to antibiotics can complicate the implementation of appropriate procedures. ^{21,22} Isolating this pathogen can challenge the assessment of its clinical significance. Microbiological studies indicate that *Corynebacterium* spp. are usually susceptible to vancomycin, amoxicillin, cephalosporins and penicillin. ^{7,23-24}

KD is the second most common systemic vasculitis in children, nevertheless, it remains a rare disease. No diagnostic test has been developed for this disease, and diagnosis is based on clinical criteria and laboratory test results. In 2019 experts of the European initiative Single Hub and Access point for pediatric Rheumatology in Europe (SHARE)⁸ recommended that the AHA diagnostic criteria⁹ should be used for complete and incomplete KD (Table 2). As recommended the diagnosis of KD should be considered in any child with a febrile illness and evidence of inflammation,

particularly if it persists longer than four days. In children presenting with less than 5 out of 6 criteria for KD (incomplete KD), with evidence of unexplained systemic inflammation, an echocardiogram should be considered.

In the presented case, the patient met the criteria for KD and incomplete KD. Ultimately, the infection was diagnosed. Laboratory tests in our patient revealed high levels of neutrophils, which are an important component of the innate immune system and are the first line of defense against bacterial infections.²⁵ Corynebacterium pseudodiphtheriticum activates Toll-like receptors (TLRs), which leads to the production of cytokines, mainly interleukin-6 (IL-6) and interleukin-1ß (IL-1ß).26 The secretion of inflammatory cytokines and histamine leads to the recruitment of immune cells, and in response to their growth, transcription of the CRP gene is induced, which can be increased in bacterial infections even 100-fold.^{27,28} Invasive strains of non-diptheria Corvnebacterium spp. have an ability to bind fibronectin and fibrinogen, as well as to form biofilms. Corynebacterium pseudodiphtheriticum is able to invade human epithelial type 2 (HEp-2) cells and remain detectable within 24 h post-infection. This suggests a potential mechanism that enables escape from immune system-mediated response.^{29,30} High levels of NT-proBNP in C. pseudodiphtheriticum infections may reflect a combination of respiratory burden, systemic inflammation, sepsis-related cardiac dysfunction, and potential renal impairment. They are a marker of both the severity of the infection and its impact on the entire body.^{31,32}

The targeted treatment resulted in the disappearance of the disease symptoms and normalization of parameters. Therefore, the diagnosis of KD and appropriate treatment administration remains a challenge for pediatricians, cardiologists and rheumatologists. Another topic still being investigated is infections as factors associated with KD^{10,33–35} The theory of a bacterial origin of KD is supported by the similarity of the disease course to scarlet fever and toxic shock syndrome, both determined by superantigens. However, no antibodies against superantigens responsible for toxic shock syndrome were found in the serum of patients suffering from KD, which does not seem to confirm this hypothesis.¹⁰

However, it should be emphasized that following the SHARE recommendations, in cases where evidence of infection is observed in patients with KD, both diseases should be treated.⁸

5. CONCLUSIONS

- (1) Corynebacterium species should be considered a clinically important pathogen, especially when cultured in patients with immunosuppression or systemic diseases.
- (2) The ability of *Corynebacterium* other than *C. diphtheriae* to mimic the symptoms of diphtheria complicates diagnosis and treatment.
- (3) Further research on the virulence factors, antibiotic resistance patterns, and epidemiology of *Corynebacterium* is necessary to develop targeted therapeutic strategies.

- (4) Performing additional tests and early detection of the causative pathogen is the key to achieving a satisfactory treatment outcome. An important aspect to remember is the significant role of vaccinations.
- (5) Greater state control of mandatory vaccinations is essential to prevent diseases similar to the one that appeared in the case of the patient described.

Conflict of interest

None declared.

Funding

None declared.

Ethics

We declare no ethical conflicts.

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