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URTICARIA CAUSED BY
ARCANOBACTERIUM HAEMOLYTICUM. DIAGNOSTIC
AND THERAPEUTIC FAILURES

ABSTRACT: We presented a case of seventeen-year-old girl exhibiting mild symp-
toms of sore throat, a marked urticarial rash and heavy desquamations of the skin on palms
and soles. According to the antibiogram and diagnosis of Streptococcus non A non B group
obtained in routine laboratory procedure, the patient was treated with penicillin; however,
ineffectively. Escalation of urticaria and failure of the initial penicillin therapy shifted the
diagnosis towards exanthema toxoalergicum and thus to treatment with corticosteroids and
antihistamines, yet with no improvement. The culture was repeated with a new specimen.
Diagnosis was made according to the specific pattern in a double CAMP test, and confir-
med by the ApiCoryne diagnostic set (BioMerieux).

With respect to cultural traits, the isolate mimicked Streptococcus pyogenes, yet de-
vloping specific pattern in a double CAMP test that directed our diagnosis towards
coryneform microorganisms. The diagnosis of Arcanobacterium haemolyticum was confir-
med with 99.9% probability rate and $T = 0.75$.

KEY WORDS: Arcanobacterium haemolyticum, exanthema, diagnosis, erythromycin
therapy

INTRODUCTION

Arcanobacterium haemolyticum (A. haemolyticum) is one of the four spe-
cies of the genus Arcanobacterium [Ramos, 1977] exhibiting all characteri-
istics of irregular non-sporulating Gram-positive rods [Holt, 1994; Funke, 1997].

Man is the primary reservoir and the most frequently affected species, though there are reports of isolates of animal origin [Richardson and Smith, 1968; Roberts, 1969; Younan and Drescher, 1996; Suvajdžić et al., 2002; Suvajdžić et al., 2002]. Young adults are the most frequently affected population [Miller et al., 1986; Slaaridge, 1989; Carlson et al., 1994; Nyman and Banch, 1984], but there are reports of infection in children [Karpathios et al., 1992]. In immunocompromised individuals, infections of the upper respiratory tract are mostly induced [MacLean et al., 1946; Mackenzie et al., 1995; Chalupa et al., 1995], which may be associated with a rash [Banc and Nyman, 1986] of the scarlatiniform [Carlson et al., 1994] or urticarial type and enlarged lymph nodes, particularly in the neck region [Banc and Nyman, 1984]. Clinical symptoms mimicking rash fevers of viral etiology and undefined allergic events often result in overlooking this organism in a suspect diagnosis. Due to its close similarity to the beta-hemolytic species of the genus Streptococcus and nondescript colonial architecture, it is often misidentified in routine practice, though its pathogenic potential is well established as early as 1946 [MacLean et al., 1946].

MATERIAL AND METHODS

Study subject

The patient was a seventeen-year-old girl without personal or family history of chronic disease or allergy. She was admitted for examination because of a skin rash in the chest region. The patient was in good general condition, with slightly increased body temperature (37.3°C) and without any subjective complaints.

Physical examination revealed a light-pink macular rash, circular in shape, with no skin elevation, with distinct maculae surrounded by unchanged skin. Signs of mild rhinopharyngitis were evident, as well as a slight enlargement of a submental lymph node (about 1 cm in diameter). There were no changes on other organs and organ systems. The presentations were characterized as Rubella and symptomatic therapy was recommended.

After 2—3 days, changes of rash appearance and distribution became obvious, extending across the body and extremities, being most prominent at the lower abdomen. Efflorescences were maculopapular, slightly elevated from the skin level, red, oval, distinct or convergent (particularly on the extremities), different in size, and with zones of healthy (unchanged) skin amongst them. Pronounced pruritus was present. Body temperature was slightly increased (37.3°C), the pharynx was hyperaemic without enanthema, and the submental lymph node was unchanged with respect to the previous examination.

Laboratory findings showed a slightly increased sedimentation rate, 20 mm/hour. Blood count revealed leucocytosis 15x10^3/l with prevailing neutro-
phyles (87%), fibrinogen 4.0. Billirubin, transaminase and gamma GT values were within the limits of normal ones. Electrophoresis of serum proteins was not performed due to technical reasons.

**Complement fixation test (CFT):** Adeno 1/16, *Mycoplasma pneumoniae* < 1/4, *Chlamydia trachomatis* (group Ag) < 1/2, Paul Bunell negative

**Enzyme Linked Immunosorbent Assy (ELISA):** IgM Rubella negative

**Pharyngeal swab:** *Streptococcus* non A non B group

**Recommended therapy —** Fenoxymethylpenicillin (*Cliacl®*).

The therapy applied in the first week was ineffective.

The efflorescences gradually resolved over a period of seven days, but new ones of the same characteristics occurred in other skin areas. Around day 12 after the commencement of the rash, discrete scaling of palms was noted, progressing to massive desquamation of large epidermal areas within 2—3 days. Palms and soles were extremely painful to palpation.

Skin changes were characterized as *exanthema toxoallergicum* by the epidemiologist and dermatologist. The dermatologist suggested antihistaminic therapy with terfenadine (*Bronal®*) and corticosteroids (*Dexason®* tb.). The therapy was administered during the second week of illness, without any improvement with respect to skin changes.

In the third week of illness, the rash gradually diminished and desquamation of palms and soles ended. The overall condition of the patient was good, except for the malaise and fatigue. The patient was referred by his physician to the microbiology laboratory of the Department of Pharmacy with the aim of receiving specific therapy. In that respect, the pharyngeal swab was repeated, revealing presence of *Arcanobacterium haemolyticum*. We suggested a therapy with erythromycin, 500 mg, 2 times per day, during 7 days. The therapy was administered in the third week of illness. Improvement occurred 2 days following the administration of erythromycin.

**MICROBIOLOGICAL METHODS**

The pharyngeal swab was simultaneously inoculated with and without growth lines of *Staphylococcus aureus* (2 plates of each). Subcultures were cultivated on two thioglycollate and one nutrient broth. Thioglycolates were incubated at 37 and 44°C, and the nutrient broth was kept in refrigerator at +4°C. After 48 hours, thioglycolates were subcultured onto three blood agars, which were incubated aerobically, anaerobically and microaerophilically. The nutrient broth was incubated at +4°C during 7 days. Subcultures on blood agar were made daily.

Preparations of primoisolates and subcultures were Gram stained, and the grown colonies examined in catalase, oxidase and esculin tests. “Double CAMP test” (*Rhodococcus-a ureus* CAMP at the same blood agar plate) [4, 18] was performed, and possibility of bacterial growth in the presence of bile acids (0.33% cholic and 0.33% monoketocholic acid) was investigated. Ability of agglutination with streptococcal serums in the commercial Slidex Strepto Bio-Merieux set (Bio Merieux, Marcy-l’Etoile, France) was also tested. Final diag-
nosis was performed with the API Coryne (Bio Merieux, Marcy-l’Etoile, France) diagnostic kit, and later evaluated using a software program from the same manufacturer.

RESULTS

In all incubation and temperature conditions, small hemolytic colonies grew on blood agar, which strongly resembled beta haemolytic cocci. However, they did not agglutinate with any of streptococcal diagnostic sera in the SLIDEX Strepto-kit (BioMerieux, Marcy-l’Etoile, France). Further thorough investigation of the subcultures revealed Gram-positive rods in young cultures (up to 18 hours of age), which, with age, changed their morphology towards pleomorphism and polychromasia. The tendency towards Gram-labile, granulated, irregular coccoid form culminated as early as in 24 hours. Oxydase, catalase and esculin tests were negative. In a double CAMP test the isolate produced a strong restriction of haemolysis of *S. aureus* and a marked synergistic haemolysis with *Rhodococcus equi*, with a characteristic “open umbrella” shaped pattern (Figures 1, 2 and 3). Biochemical characteristics are summarized in Table 1.

![Fig. 1 — CAMP phenomenon on day 1 of incubation](image)
Fig. 2 — CAMP phenomenon on day 2 of incubation

Fig. 3 — CAMP phenomenon on day 3 of incubation
Note development of the specific pattern of species-specific \textit{A. haemolyticum} in a double CAMP test — synergistic haemolysis with \textit{Rhodococcus equi} ("open umbrella") and restriction of beta-haemolysis of \textit{Staphylococcus aureus}

Key Note:
Right vertical line = \textit{Staphylococcus aureus}
Left vertical line = \textit{Rhodococcus equi}
Top and bottom horizontal lines = \textit{Streptococcus agalactiae}
Two horizontal lines in the middle = \textit{Arcanobacterium haemolyticum}

Tab. 1 — Biochemical characteristics of the investigated \textit{A. haemolyticum} strain. Identification table of \% positive reaction after 24h at 35—37°C

<table>
<thead>
<tr>
<th>TEST</th>
<th>REACTION</th>
<th>INVESTIGATED STRAIN</th>
<th>IDENTIFICATION TABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIT</td>
<td>Nitrate reduction</td>
<td>0/1</td>
<td>1</td>
</tr>
<tr>
<td>PYZ</td>
<td>Pyrazinamidase</td>
<td>1/1</td>
<td>98</td>
</tr>
<tr>
<td>PyrA</td>
<td>Pyrolydonil Arylamidase</td>
<td>0/1</td>
<td>70</td>
</tr>
<tr>
<td>PAL</td>
<td>Alkaline phosphatase</td>
<td>1/1</td>
<td>85</td>
</tr>
<tr>
<td>β-GUR</td>
<td>Beta glucuronidase</td>
<td>0/1</td>
<td>36</td>
</tr>
<tr>
<td>β-GAL</td>
<td>Beta galactosidase</td>
<td>1/1</td>
<td>89</td>
</tr>
<tr>
<td>α-GLU</td>
<td>Alpha glucosidase</td>
<td>0/1</td>
<td>92</td>
</tr>
<tr>
<td>β-NAG</td>
<td>N-A-Glucosaminidase</td>
<td>1/1</td>
<td>89</td>
</tr>
<tr>
<td>ESC</td>
<td>Esculin</td>
<td>0/1</td>
<td>0</td>
</tr>
<tr>
<td>URE</td>
<td>Urea</td>
<td>0/1</td>
<td>0</td>
</tr>
</tbody>
</table>

The result was red using the BioMerieux software program (Bio Merieux, Marcy-l’Etoile, France), being \textit{A. haemolyticum}, with the probability rate of 99.9\% and $T = 0.75$. The only parameter that departed from the identification table was alpha glucosidase negativity, which should have been positive in 92\%.

DISCUSSION

\textit{A. haemolyticum} was isolated in a 17-year-old patient. According to the results of \textit{Miller et al.} (1986), this organism is mostly isolated in teenagers and younger adults. This was also confirmed by \textit{Claridge} (1989) and \textit{Carlson et al.} (1994).

The organism was isolated from the pharynx, which was confirmed as the predilection site by several authors [\textit{MacLean et al., 1946}; \textit{MacKenzie, 1995}; \textit{Chalupa et al., 1995}].

The rash was the dominant finding, preceding sore throat, rather urticarial then scarlatiniform, and accompanied by pruritus. Skin scaling followed by desquamation of palms and soles was obvious. These changes are not typical for pharyngitis caused by \textit{A. haemolyticum} [\textit{Wagner, 1991}] but there are several descriptions in the literature [\textit{MacKenzie, 1995}; \textit{Chalupa et al.}, 1995].
The initial report described one of 12 patients with rash attributed to allergy, diagnosed as exanthema toxoallergicum, same as our patient [MacLean et al., 1946].

*A. haemolyticum* was isolated in abundance, without presence of other potential pathogenic bacterial agents. Streptococcus-like colonies with coryneform microscopic appearance were suggestive of *Arcanobacterium / Actinomyces* spp. The diagnosis was made according to the characteristic pattern in the double CAMP test. Haemolysis restriction of *S. auerus* and synergism with the equi factor of *R. equi* is pathognomonic for *A. haemolyticum* [Claridge and Spiegel, 1995; Suvajdžić et al., 1998], which was confirmed by the APICoryne diagnostic set program (BioMerieux, Marcy-l’Etoile, France).

By the available methodology, viral agents *Chlamydia trachomatis* and *M. pneumoniae* were excluded, thus we believe *A. haemolyticum* is the causal agent of the described status. The patient was treated with penicillin that, in spite of its good activity *in vitro*, did not result in any improvement. This result is consistent with reports of Banck, Nyman and Osterlund [Banck and Nyman, 1986; Nyman and Banck, 1984; Osterlund, 1995; Nyman and Banck, 1990].

**CONCLUSION**

Prompt etiological diagnosis is of crucial importance for clinicians, protecting patients and physicians from diagnostic and therapeutic failures (in this case the patient could have been spared from cortisone and antihistaminic therapy). In cases of a rash of unclear etiology accompanied by pharyngitis, we suggest excluding the presence of *A. haemolyticum*. In the case that the microbiology laboratory does not have relatively expensive diagnostic sets (BioMerieux or else), diagnosis can be made at the cost of a single blood agar Petri-plate, using characteristic pattern in a double CAMP test, which is species-specific.

**REFERENCES**


\textbf{УРТИКА ИЗАЗВАНА \textit{ARCANOBACTERIUM HAEMOLYTICUM}-ОМ. ДИЈАГНОСТИЧКА И ТЕРАПИЈСКА ЛУТАЊА*}

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Резиме

\textit{Arcanobacterium haemolyticum} се ретко изолује као узрок фарингитиса који је у 30% случајева праћен егзантемом. У рутинској пракси обично се превиђа јер клинички имитира алеријски, постстриптококни или осип вирусне етиологије. Приказујемо случај седамнаестогодишње девојке која је имала блаће симптоме упале грађе праћене наглашеним уртicatorијалним rashом са последицама десквамацијом коже стопала и дланова. Водећи се резултатом антибиограма и бактериолошком дијагнозом \textit{Streptococcus nonA nonB} групе пацијент је тетриран пеницилинином али безуспесно. Ескалација уртике након увођења пеницилина завела је клиничара ка дијагнози \textit{exanthema toxoalergicum}. Стога је настањен третман антихистаминима и кортикостероидима такође безуспесно. Поново узет брис је бактериолошки обрађен у циљу искључивања коринеформних бактерија. На основу специфичног резултата у двоструком САМР тесту посумњано је на \textit{Arcanobacterium haemolyticum}, а дијагноза је потврђена дијагностичким сетом ApiCore - diagnostic set. Софтверски програм истих произвођача дијагнозу \textit{Arcanobacterium haemolyticum} је оценено као одличну, са вероватноћом идентитета 99,9% уз степен сигнурности $T = 0.75$. Оваква дијагноза сугрена је еритромицинску терапију — 500 mg 2 пута дневно у трајању од 7 дана што је довело до потпуног излечења пацијента. Сходно томе у случајевима раша нејасне етиологије удржава се са фарингитисом сугренише мо искључивање \textit{Arcanobacterium haemolyticum}. Прецизна микробиолошка дијагноза доступна је свакој рутинској лабораторији уколико се уместо обичног САМР теста у случају бета хемолитичких колонија стрептококног изгледа користи двоструки САМР тест.

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