 Concurrent diphtheria and infectious mononucleosis: difficulties for management, investigation and control of diphtheria in developing countries

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We report a case of concurrent diphtheria and infectious mononucleosis in an 11-year-old Brazilian child. Two days after specific treatment for diphtheria was started the patient was discharged following clinical recovery. This case highlights the difficulties in the clinical diagnosis of diphtheria in partially immunized individuals, and for the management and control of diphtheria in developing countries.

Introduction

Nowadays, diphtheria can occur in children and adults with a history of incomplete immunization, in whom the disease can be difficult to diagnose. Investigation of these cases can have considerable implications for health services. There has been a noticeable increase in the number of patients presenting with one of the toxin-induced complications of the illness without any prominent evidence of local pharyngeal infection or without presentation of systemic toxin-induced complications (Perkins et al., 2010).

Although a vaccine-preventable disease, diphtheria is still endemic in all continents (Jacob John, 2008; Bonmarin et al., 2009; Honma et al., 2009), especially in developing countries. As for several countries from Europe and beyond (Wagner et al., 2011), the epidemiology of Corynebacterium diphtheriae infections in Brazil remains poorly understood (Mattos-Guaraldi et al., 2003; Hirata et al., 2008).

Diphtheria should be strongly suspected in a probable case where the patient presents with: upper respiratory illness characterized by sore throat, low grade fever, and an adherent membrane of the tonsils, pharynx and/or nose, in whom there are signs of systemic toxicity (fever, tachycardia and weakness); without another clearly established diagnosis in areas with endemic or epidemic diphtheria; and/or who was never vaccinated or is not up-to-date with diphtheria toxoid vaccination. In Brazil, a case of diphtheria is classified as confirmed when a clinically compatible case is laboratory confirmed with the isolation of C. diphtheriae or has an epidemiological link to a laboratory-confirmed case. For probable cases that are considered to have a lower probability for diphtheria, the physician should consider other diagnoses [Portal Saúde: Difteria, Ministério da Saúde, 2010 – http://webcache.googleusercontent.com/custom?q=cache:LyQzN9zOMB0J:portal.saude.gov.br/portal/saude/visualizar_texto.cfm?idtxt=3D26994+ficha+difteria (http://portal.saude.gov.br/portal/saude/visualizar_texto.cfm?idtxt=3D26994)].

Case report

Herein, we report a case of coincidental diphtheritic membrane and infectious mononucleosis (IM) in an 11-year-old

Abbreviations: DAT, diphtheria antitoxin; IM, infectious mononucleosis.
Brazilian boy with a history of Kawasaki disease at the age of 7 years and who had only partial immunization during childhood for diphtheria. Aside from the first three doses of vaccine for diphtheria, he had no previous history of booster doses given since 4–6 years of age.

The patient was admitted at a public outpatient care centre 5 days after the onset of a membranous tonsillo-pharyngitis. The primary care physician clinically diagnosed the illness as streptococcal pharyngitis and empirically treated the patient with penicillin G benzathine. However, the antibiotic therapy did not lead to a clinically significant improvement.

On the ninth day of illness (5 September 2008) the patient presented with low fever (37.8°C), sore throat, enlargement of a single node with subcutaneous swelling on the right, in addition to a copious greyish-white discharge and a firmly adherent membrane on the right tonsil, as illustrated in Fig. 1. A diagnosis of diphtheria was suspected upon physical examination in a teaching hospital located in the Rio de Janeiro metropolitan area [Hospital Universitário Pedro Ernesto (HUPE), Rio de Janeiro, Brazil], and the Bacteriology Section of the Public Health Centre in Rio de Janeiro (Noel Nutels, LACEN-SEDC, Rio de Janeiro, Brazil) was immediately contacted for direct bacterioscopy examination, isolation and identification of C. diphtheriae from throat swabs. The case was notified to the Brazilian Department of Health authorities after a large number of pleomorphic Gram-positive bacilli were seen through direct bacterioscopy.

Upon admission to the paediatric isolation unit for infectious diseases [Hospital Universitário Pedro Ernesto (HUPE)], an appropriate sensitivity test of the patient was performed, and 60 000 U diphtheria antitoxin (DAT) and intravenous crystalline penicillin G (170 000 U) were given.

Laboratory results included: leukocytosis, 12 870 leukocytes μl⁻¹ with 2% bands; lymphocytes, 67.6% with less than 1% atypical; platelet count, 184 000 platelets μl⁻¹; haematocrit, 41.0%; haemoglobin, 13.7 g dl⁻¹; troponin, negative; creatine kinase, 229 U l⁻¹ and creatine kinase isoenzyme MB, 30 U l⁻¹; creatinine, 0.5 ng ml⁻¹; urea nitrogen, 27 mg l⁻¹; serum aminotransferases (179 U alanine aminotransferase l⁻¹ and 221 U aspartate transaminase l⁻¹); and 1.247 U lactate dehydrogenase l⁻¹. Urinalysis was normal and blood cultures gave negative results.

On 7 September 2008, 48 h after the specific treatment for diphtheria started, the fever had progressively disappeared, and so had the pseudomembrane and oedema of the anterior cervical lymph nodes. On 9 September 2008, the appearance and persistence of rare atypical lymphocytes in addition to high levels of aminotransferases until the fourth day of hospitalization suggested an Epstein–Barr virus co-infection. For this reason IgM antibodies for viral capsid antigen were also investigated.

On 10 September 2008, the laboratory reported, from the initial throat swab cultures on sheep blood agar and tellurite chocolate agar media, the presence of Gram-positive Corynebacterium-like colonies that showed positive results for C. diphtheriae biochemical identification tests, including catalase, glucose and maltose fermentation tests (Efstratiou & George, 1999), and a DNase test (Pimenta et al., 2008). However, testing for toxigenicity by the Elek test was not performed.

Epstein–Barr IgM antibody testing gave positive results, suggesting a primary Epstein–Barr virus co-infection. At this moment, the patient presented as having a good general state of health and was sent home. On prolonged follow up, there were still no symptoms, signs or laboratory results suggesting peripheral neuropathy or cardiomyopathy. Electrocardiograms (8, 10 and 15 September 2008), a transthoracic echocardiogram (19 September 2008) and electromyography (18 September 2008) were all normal. Contact tracing for diphtheria was carried out but no probable or possible sources were found.

Discussion

The tendency to disregard pathogens such as C. diphtheriae can lead to delayed or inappropriate therapy. In Brazil, at present, most physicians have little experience in diagnosing and treating diphtheria. In addition, individuals with less schooling, which is frequently associated with various other unfavourable social conditions, are less aware of their health and show less self-care, causing a delay in seeking health care, which results in late diagnosis and treatment (Mattos-Guaraldi et al., 2003; Pelaquin et al., 2007). In the case presented here, difficulties were noted in seeking health care (5 days after the onset of a membranous tonsillo-pharyngitis) and in clinically diagnosing diphtheria (9 days after the onset of the illness) in an 11-year-old child. In other investigations several cases were also

**Fig. 1.** Greyish-white discharge and an adherent membrane on the right tonsil of a partially immunized 11 year-old boy presenting concurrent diphtheria and IM.
identified with a delay in seeking health care, diagnosing the illness and initiating appropriate therapy (Mattos-Guaraldi et al., 2003; Perkins et al., 2010).

Patients who have probable or confirmed respiratory diphtheria are eligible to receive DAT. The final decision to administer DAT to a patient lies with the treating physician. Specific treatment with DAT and antibiotics should be initiated immediately without waiting for bacteriological confirmation (Tiwari & Clark, 2008).

The rarity of cases and the expense and complexity associated with laboratory diagnosis provided many countries with an indication to cease screening clinical specimens for *C. diphtheriae*. Laboratory confirmation is not utilized to validate clinical data in many opportunities (Glinyenko et al., 2000). In some developing countries it is common to base a presumptive diagnosis upon the initial clinical features of the illness and bacteriological examination of lesions.

Although the microscopy examination of a direct smear of a clinical specimen is not sufficiently accurate to diagnose diphtheria for health authorities, in some cases it is the only method available to the microbiologist or infectious diseases physician to alert others to the possibility of clinical diphtheria (Mattos-Guaraldi et al., 2003).

Appropriate management of acute pharyngitis depends on the proper use and interpretation of clinical findings, throat cultures and rapid antigen-detection tests (McIsaac et al., 2004). Diseases that can occasionally produce a similar membranous pharyngitis include streptococcal pharyngitis and IM (Haight & Holden, 1982; Taga et al., 2001).

The difficulty of differentiating certain clinical forms of IM from diphtheria has been well recognized for decades (Chretien & Esswein, 1976). Making an accurate diagnosis is especially difficult in cases of concurrent diphtheria and IM. These facts may explain the small number of previous cases of concurrent IM and diphtheria observed among adults.

### Table 1. Clinical and laboratory aspects observed in the three cases of concurrent IM and diphtheria

<table>
<thead>
<tr>
<th>Symptom/feature</th>
<th>First case (in the literature)*</th>
<th>Second case (in the literature)†</th>
<th>Third case (this study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>Canada, 1982</td>
<td>UK, 2009</td>
<td>Brazil, 2009</td>
</tr>
<tr>
<td>Age/sex</td>
<td>21-year-old/male</td>
<td>Teenager</td>
<td>11-year-old/male</td>
</tr>
<tr>
<td>Immunization for diphtheria during childhood</td>
<td>Complete</td>
<td>Incomplete</td>
<td>Incomplete</td>
</tr>
<tr>
<td>No. of days with symptoms before hospitalization</td>
<td>10</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Fever</td>
<td>39.5 °C</td>
<td>ND</td>
<td>37.8 °C</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Yes; difficulty in swallowing</td>
<td>Yes; severe throat, pustular tonsils and abdominal pain in the right upper quadrant</td>
<td>Yes; difficulty in swallowing</td>
</tr>
<tr>
<td>Pseudomembrane formation</td>
<td>Greyish-white discharge and membrane on the posterior pharyngeal wall</td>
<td>Absent</td>
<td>Greyish-white discharge and firmly adherent membrane on the right tonsil</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Tender diffuse cervical lymphadenopathy in both anterior and posterior triangles</td>
<td>ND</td>
<td>Swollen neck; single node with subcutaneous swelling on the right</td>
</tr>
<tr>
<td>Total leukocytosis</td>
<td>21 800 leukocytes μl⁻¹</td>
<td>ND</td>
<td>12 870 leukocytes μl⁻¹</td>
</tr>
<tr>
<td>Band</td>
<td>21 %</td>
<td>ND</td>
<td>2 %</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>55 %</td>
<td>ND</td>
<td>67.6 %</td>
</tr>
<tr>
<td>Monocytes</td>
<td>4 %</td>
<td>ND</td>
<td>10.2 %</td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>14 %</td>
<td>ND</td>
<td>&lt;1 %</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>610 U l⁻¹</td>
<td>ND</td>
<td>1247 U l⁻¹</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>101 U l⁻¹</td>
<td>ND</td>
<td>179 U l⁻¹</td>
</tr>
<tr>
<td>Diagnosis of IM</td>
<td>Positive monospot test on the 13th day of illness</td>
<td>Positive monospot test on the 8th day of illness</td>
<td>Positive Epstein–Barr viral capsid antigen IgM specific antibodies test on the 9th day of illness</td>
</tr>
<tr>
<td>Initial therapy</td>
<td>Amoxicillin</td>
<td>i.v. penicillin</td>
<td>Penicillin and amoxicillin</td>
</tr>
<tr>
<td>Rash due to amoxicillin</td>
<td>Yes</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>Specific treatment for diphtheria</td>
<td>On day 5 after admission was given 80 000 U DAT and i.v. penicillin</td>
<td>Until 3 days after admission was given i.v. penicillin</td>
<td>On day of admission was given 60 000 U DAT and i.v. penicillin</td>
</tr>
<tr>
<td>Resolution of the case</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

i.v., Intravenous; ND, not described.

*Haight & Holden (1982).
†Perkins et al. (2010).
reports available in the medical literature of IM and a coincidental pharyngeal infection with *C. diphtheriae* (Haight & Holden, 1982). We found only two other cases of concurrent diphtheria and IM described in the published medical literature (Haight & Holden, 1982; Perkins et al., 2010). Clinical and laboratorial aspects observed in the three cases (our case and the two mentioned above) are summarized in Table 1. In all the reports, the patients gave a history of immunization against diphtheria during early childhood.

The fact that our patient was partially immunized against diphtheria (did not receive booster doses of diphtheria toxoid) has possibly contributed to the establishment of a localized clinical form of the disease. Similar to the case described in the UK (Perkins et al., 2010), there was also a delay in the diagnosis of diphtheria partly due to the low level of clinical suspicion. Different from the case reported in the UK, the presence of a firmly adherent membrane on the right tonsil, enlarged anterior cervical lymph nodes and oedema of soft tissues strongly demonstrated the action of diphtheria toxin. As for the case in Canada (Haight & Holden, 1982), a sustainable resolution of the disease occurred with the administration of DAT and intravenous penicillin.

**Conclusion**

We report here a case of concurrent diphtheria and IM in a child living in the metropolitan area of Rio de Janeiro, Brazil. Data illustrate the difficulty in the clinical diagnosis of diphtheria in partially immunized individuals. Attainment of the goal of eliminating diphtheria among persons of all age groups will depend on the maintenance of a high level of clinical awareness of classical and atypical cases of the disease and the screening of clinical specimens for *C. diphtheriae*, especially in the developing world.

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**References**


