Case Report

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

A. L. Mattos-Guaraldi,¹ P. V. Damasco,^{2,3} D. L. R. Gomes,^{1,4}
M. G. Melendez,³ L. S. Santos,¹ R. S. Marinelli,⁵ F. Napoleão,^{1,5}
P. S. Sabbadini,¹ C. S. Santos,¹ L. O. Moreira⁶ and R. Hirata, Jr¹

Correspondence

A. L. Mattos-Guaraldi
guaraldi@uerj.br

¹Disciplina de Microbiologia e Imunologia, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil

²Disciplina de Doenças Infecciosas e Parasitárias, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil

³Disciplina de Doenças Infecciosas e Parasitárias, Universidade do Rio de Janeiro, Rio de Janeiro, Brazil

⁴Instituto Federal de Educação, Ciência e Tecnologia do Rio de Janeiro, Rio de Janeiro, Brazil

⁵Laboratório Central Noel Nutels, LACEN-SESDEC (Laboratório Central de Saúde Pública – Secretaria de Estado de Saúde e Defesa Civil), Rio de Janeiro, Brazil

⁶Disciplina de Patologia Geral, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil

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.

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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:LyQzN9zOBM0J:portal.saude.gov.br/portal/saude/visualizar_texto.cfm%3Fidtxt%3D26994+ficha+difteria (http://portal.saude.gov.br/portal/saude/visualizar_texto.cfm?idtxt=26994)].

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.

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.

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

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 (Glinenko *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

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

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

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

- Bonmarin, I., Guiso, N., Le Flèche-Matéos, A., Patey, O., Patrick, A. D. & Levy-Bruhl, D. (2009). Diphtheria: a zoonotic disease in France? *Vaccine* **27**, 4196–4200.
- Chretien, J. H. & Esswein, J. G. (1976). How frequent is bacterial superinfection of the pharynx in infectious mononucleosis? Observations on incidence, recognition and management with antibiotics. *Clin Pediatr (Phila)* **15**, 424–427.
- Efstratiou, A. & George, R. C. (1999). Laboratory guidelines for the diagnosis of infections caused by *Corynebacterium diphtheriae* and *Corynebacterium ulcerans*. *Commun Dis Public Health* **2**, 251–257.
- Glinenko, V. M., Abdikarimov, S. T., Firsova, S. N., Sagamonjan, E. A., Kadirova, R., Nuorti, J. P. & Strebel, P. M. (2000). Epidemic diphtheria in the Kyrgyz Republic, 1994–1998. *J Infect Dis* **181** (Suppl. 1), S98–S103.
- Haight, K. & Holden, F. A. (1982). When infections co-exist: infectious mono and diphtheria. *Can Fam Physician* **28**, 785–788.
- Hirata, R., Jr, Pereira, G. A., Filardy, A. A., Gomes, D. L., Damasco, P. V., Rosa, A. C., Nagao, P. E., Pimenta, F. P. & Mattos-Guaraldi, A. L. (2008). Potential pathogenic role of aggregative-adhering *Corynebacterium diphtheriae* of different clonal groups in endocarditis. *Braz J Med Biol Res* **41**, 986–991.
- Honma, Y., Yoshii, Y., Watanabe, Y., Aoki, N., Komiya, T., Iwaki, M., Arai, H., Arakawa, Y., Takahashi, M. & Kimura, H. (2009). A case of afebrile pneumonia caused by non-toxigenic *Corynebacterium diphtheriae*. *Jpn J Infect Dis* **62**, 327–329.
- Jacob John, T. (2008). Resurgence of diphtheria in India in the 21st century. *Indian J Med Res* **128**, 669–670.
- Mattos-Guaraldi, A. L., Moreira, L. O., Damasco, P. V. & Hirata, R., Jr (2003). Diphtheria remains a threat to health in the developing world – an overview. *Mem Inst Oswaldo Cruz* **98**, 987–993.
- Mclsaac, W. J., Kellner, J. D., Aufricht, P., Vanjaka, A. & Low, D. E. (2004). Empirical validation of guidelines for the management of pharyngitis in children and adults. *JAMA* **291**, 1587–1595.
- Pelaquin, M. H. H., Souza e Silva, R. & Ribeiro, S. A. (2007). Factors associated with death by tuberculosis in the eastern part of São Paulo city, 2001. *J Bras Pneumol* **33**, 311–317.
- Perkins, S., Cordery, R., Nixon, G., Abrahams, A., Andrews, J., White, J., Efstratiou, A. & Anakari, S. (2010). Investigations and control measures following a non-travel-associated case of toxigenic *Corynebacterium diphtheriae*, London, United Kingdom, December 2009–January 2010. *Euro Surveill* **15**, pii=19544.
- Pimenta, F. P., Souza, M. C., Pereira, G. A., Hirata, R., Jr, Camello, T. C. & Mattos-Guaraldi, A. L. (2008). DNase test as a novel approach for the routine screening of *Corynebacterium diphtheriae*. *Lett Appl Microbiol* **46**, 307–311.
- Taga, K., Taga, H. & Tosato, G. (2001). Diagnosis of atypical cases of infectious mononucleosis. *Clin Infect Dis* **33**, 83–88.
- Tiwari, T. & Clark, T. (2008). Use of Diphtheria Antitoxin (DAT) for Suspected Diphtheria Cases, IRB # 4167, BB IND 11184:112. Atlanta, GA: Centers for Disease Control and Prevention. http://www.cdc.gov/vaccines/vpd-vac/diphtheria/dat/downloads/protocol_032504.pdf.
- Wagner, K. S., White, J. M., Neal, S., Crowcroft, N. S., Kuprevičienė, N., Paberza, R., Lucenko, I., Jöks, U., Akbaş, E. & other authors (2011). Screening for *Corynebacterium diphtheriae* and *Corynebacterium ulcerans* in patients with upper respiratory tract infections 2007–2008: a multicentre European study. *Clin Microbiol Infect* **14**, 519–525.