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Nasopharyngeal *Corynebacterium ulcerans*: a different diptheria

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Abstract
A case of toxigenic *Corynebacterium ulcerans* infection is presented. The diagnosis was delayed and no anti-toxin administered. A nasopharyngeal biopsy was complicated by severe haemorrhage necessitating a post nasal pack. A brief review of the pathology and treatment of *Corynebacterium ulcerans* is given.

Introduction

The effectiveness of the immunization programme has reduced the incidence of diphtheria in England and Wales from 46,281 in 1941, to only four in 1986 (Anon, 1987). The cases presenting to doctors are also likely to be ameliorated by immunization and less easily diagnosed. Diagnosis is usually made on the clinical appearance of the pharyngeal membrane and confirmed by microbiological means. However, the differential diagnosis of a pseudomembraneous pharyngeal exudate includes infectious mononucleosis, streptococcal pharyngitis, viral exudative pharyngitis, fusospirochaetal infections and even acute pharyngeal candidiasis.

We present a case of the rare *Corynebacterium ulcerans* affecting principally the postnasal space which gave some difficulty in diagnosis.

Case report

A previously healthy 44-year-old female was referred with a three-day history of a sore throat and increasing dysphagia. At presentation, she was unable to tolerate solids and could only swallow liquids with difficulty. On examination she had a generalized pharyngitis with an erythematous and somewhat oedematous soft palate and some small areas of slough on the uvula. There was no palpable cervical lymphadenopathy. Her temperature was 38°C, pulse 100/min white blood count 8.3×10^9/l and haemoglobin 11.3 gm/dl. A lateral soft tissue X-ray of her neck and chest films were unremarkable. She was admitted to the ward where a throat swab and blood cultures were taken and intravenous fluids and Augmentin commenced. In view of the exudate on the uvula the microbiology laboratory was alerted to the possibility of diphtheria, but unfortunately, due to a misunderstanding the swabs were placed in the fridge where they remained for the weekend.

There was little subsequent improvement and the patient remained pyrexial with a white count of 3.9×10^9/l. The patches of slough had coalesced to form a definite whitish membrane which was now encasing the uvula (Fig. 1) and appeared to be arising from the postnasal space. There was still no cervical lymphadenopathy. In view of the negative swab and blood culture results and increasing slough an examination under anaesthesia of the postnasal space and biopsy was undertaken.

This revealed extensive slough throughout the whole of the nasopharynx, the upper aspect of the soft palate and uvula, but not the choanae. The slough came away easily but a substantial haemorrhage arising from a wide area of the posterior pharyngeal wall resulted which eventually necessitated the insertion of a postnasal pack. The rest of the pharynx, larynx and upper oesophagus appeared normal with no evidence of membrane. In the recovery room the patient had a respiratory arrest which required re-intubation. She spent the night in the High Dependency Unit but showed no further respiratory irregularity.

The postnasal pack was removed the following day and there was no further bleeding. Post-operatively her condition improved, and by the third post-operative day she was apyrexial and eating normally.

Histology from the postnasal space mucosal biopsy showed ulceration of the epithelium with evidence of sinus histiocytosis and reactive hyperplasia in the underlying lymphoid tissue. There was no evidence of granulomata and fungal stains were negative. The slough showed fibrin only.

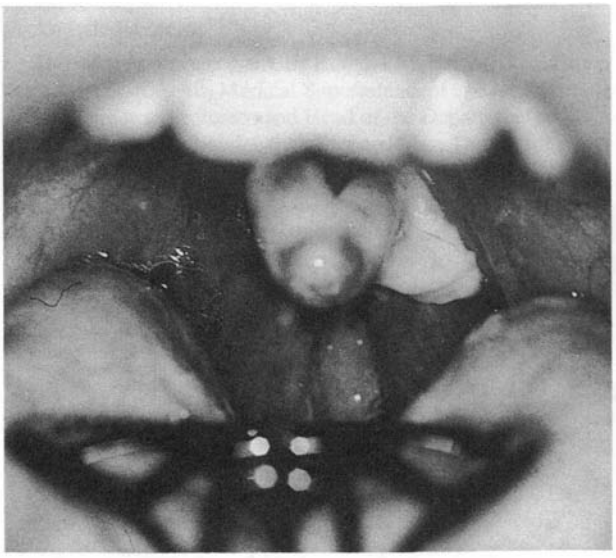

Fig. 1

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Six days post-operatively a toxigenic strain of *Corynebacterium ulcerans* was isolated from the postnasal space slough. She has made a complete recovery with no detectable abnormalities on subsequent E.C.G.'s, chest X-ray and neurological examination.

Discussion

Corynebacterium ulcerans (*C. ulcerans*), was first described following isolation from human throat lesions by Gilbert and Stewart in 1927 and appears to be genetically distinct from *C. diphtheria* and *C. pseudotuberculosis* (*C. ovis*) on DNA homology studies (Groman *et al.*, 1984). *C. ulcerans* may cause mastitis in cattle. There has been an association between human infection and drinking raw cow's milk (Bostock *et al.*, 1984; Hart, 1984) and one case following the drinking of untreated goat's milk (Barrett, 1986). In our patient and in other cases, no dairy connection could be established (Pers, 1987). *C. ulcerans* may be recovered from the pharynx without symptoms or signs of illness (Stamm, 1985) but one death due to *Corynebacterium ulcerans* has been reported (Leek *et al.*, 1990).

Petrie and McLean (1934) reported the production of two distinct exotoxins, and Carne and Onon (1982) demonstrated that *Corynebacterium ulcerans* may produce these in varying proportions. One is identical to C. *diphtheria* toxin in molecular weight, biochemical action (inhibiting protein synthesis by inactivation of elongation factor 2), chromatography, clinical effect and immunology. The other is similarly identical with *C. ovis* toxin, biochemically affecting phospholipase D, sphingomyelinase and cellular permeability. There was no evidence of a third toxin specific to *C. ulcerans*.

C. diphtheria toxin may affect principally motor nerves, and anterior horn cells as well as sensory nerves, the heart and kidneys (Harnisch, 1980). Infection with *C. ulcerans* producing *C. ovis* toxin results in local suppuration and ulcer formation in guinea pigs (Carne and Onon, 1982). Thus *C. ulcerans* may produce a variable clinical picture depending on the presence and proportions of the exotoxin produced. Meers (1979) suggests that in the past cases of diphtheria due to *C. ulcerans* (especially those 'milk borne') may have been wrongly attributed to *C. diphtheria*. One of the five cases that he discusses closely matches the clinical picture of classical diphtheria, with palatal paralysis (week 3), facial paralysis and cardiomyopathy (week 6) and limb paralysis (weeks 7–10), due to the production of *C. diphtheria* toxin by *C. ulcerans*.

Definitive diagnosis of Corynebacterium infections depend on the culturing of the organisms from relevant swabs. The laboratory should be informed of the presumptive diagnosis of diphtheria to ensure rapid innoculation on culture medium as there is a gradual reduction in Corynebacterium survival in transport medium after 24 hours. Microscopy stain smears provide unacceptably high levels of both false negative and false positive diagnoses (Brooks and Joynson, 1990). Tests of toxigenicity should be performed using a modified Elek's immunodiffusion test (Davis, 1974). Biotyping has little immediate clinical relevance but is important in terms of epidemiology and contact tracing.

Besides isolation and strict bed rest the only specific treatment of Corynebacterium infections is the administration of anti-toxin to *Corynebacterium diphtheria*. This is recommended in doses ranging from 10–100 000 units in a single dose intravenously over 30 mins after testing for sensitivity. Extension of the pharyngeal pseudomembrane to the larynx warrants higher doses of anti-toxin. However, the anti-toxin is largely ineffective if administered later than 48 hours after the onset of infection as it only inactivates toxin in the blood or extra-cellular fluid. Once the toxin has entered the cell its effects cannot be reversed or prevented. As mortality increases directly with delay in the use of the anti-toxin this should be given when diphtheria is suspected clinically and laboratory confirmation of the diagnosis prior to administration is not necessary, especially where the immunization history is not clear.

Antibiotics do not alter the course, incidence of complications or outcome of corynebacterium infections (Harnisch, 1980), though penicillin (or erythromycin) is routinely administered to eliminate the organism from the upper respiratory tract and to terminate the carrier state (McCloskey, 1985).

In our patient the definitive diagnosis of *Corynebacterium ulcerans* was hampered by the delayed inoculation of the throat swab on to culture medium. It may, however, have been prudent to administer anti-toxin on clinical grounds alone.

Immunization is very important in the prognosis of diphtheria. While full immunization does not prevent the nasopharyngeal carriage of corynebacteria the incidence of the severe 'malignant' disease is 15 times less common, paralysis five times less and the fatality rate less than one-tenth of the un-immunized population (Harnisch, 1980). Our patient was immunized as a child and this may have attenuated the virulence of the infection.

The brisk haemorrhage following removal of the postnasal space slough was probably contributed to by ulceration of the underlying mucosa (confirmed histologically) due to the production of *C. ovis* toxin by *C. ulcerans*. This complication has not previously been reported in the literature.

It is tempting to speculate that the toxin production may in some way have been responsible for her respiratory arrest in the same way that sudden death has been attributed to the toxin in classical diphtheria. However, there is no supporting evidence for this and the patient recovered fully with no neurological or E.C.G. evidence of detectable abnormality.

Conclusion

Corynebacterium diphtheria infection in Britain is currently rare and *Corynebacterium ulcerans* extremely rare. However, *C. ulcerans* may produce the two toxins in varying amounts, with one toxin producing complications typical of classical diphtheria and the other local mucosal ulceration typical of *C. ovis* toxin.

This case illustrates that despite extensive immunization programmes, corynebacteria still represent an important pathogenic strain of micro-organism to man. Their successful management requires a high index of suspicion, early diagnosis and prompt action sometimes without bacteriological confirmation. The need for good communication between clinician and microbiologist is essential.

Acknowledgements

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