Case Report

Cervical spondylodiscitis with spinal epidural abscess caused by *Aggregatibacter aphrophilus*

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Spondylodiscitis caused by *Aggregatibacter aphrophilus*, formerly known as *Haemophilus paraphrophilus*, is an unusual condition and can be very difficult to diagnose. We report a case of cervical spondylodiscitis complicated by spinal epidural abscess in a 63-year-old woman, without underlying predisposing conditions. The source of infection was identified as a periodontal infection. The patient was successfully treated with systemic antibiotics.

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Case report

A 63-year-old woman was admitted to the Internal Medicine Section, University of Perugia Medical School, in January 2007 because of cervical back pain of increasing intensity, and 7 days remittent fever (39 °C). She reported progressive weakness of the left upper arm with decreased strength in her grip. The family physician had prescribed 500 mg acetaminophen orally twice a day, 75 mg diclofenac intramuscularly twice a day and 250 mg clarithromycin orally twice a day with no improvement of clinical picture. The patient had a history of mild chronic cervical back pain for several years, and a previous radiograph of the cervical spine showed chronic degenerative changes. The patient had undergone tooth extraction 3 months previously.

At the hospital admission, she was febrile (39 °C), and physical examination showed resisted neck flexion and weakness of the distal left upper extremity; cardiac auscultation demonstrated an apical murmur, 2/6 intensity. Laboratory tests showed leukocytosis (13 900 leukocytes mm⁻³ with 90 % neutrophils) and elevation of erythrocyte sedimentation rate (77 mm h⁻¹) and C-reactive protein levels (116 mg l⁻¹). After cerebral computed tomography, the patient underwent a lumbar puncture. Cerebrospinal fluid pressure was normal, and biochemical analysis revealed increased protein levels (187 mg dl⁻¹), with normal glucose and no leukocytes. A magnetic resonance imaging (MRI) scan of the cervical spine demonstrated an abnormal signal intensity at the level of C6–C7 vertebral bodies and at the intersomatic

disc. The pre-contrast sequences also demonstrated signal alterations involving the perivertebral soft tissues from C4 to T1. Gadolinium injection showed pathological enhancement of meninges from C4 to T1, and an anterior-paramedian epidural abscess at the level of the C6–C7 intersomatic disc, not compressing the spinal cord (Fig. 1). An initial empiric antimicrobial therapy, with 400 mg teicoplanin endovenously once a day and 500 mg imipenem–cilastatin endovenously three times a day, was started; Schanz collar was used for cervical spine immobilization. Electromyography showed severe acute axonal injury at the C7–C8–T1 levels. Neurosurgical evaluation excluded the need for decompressive laminectomy or debridement of infected tissues.

Cultures of the cerebrospinal fluid were negative, while blood samples (two sets from different vein punctures), collected immediately on admission in BACTEC Plus aerobic and anaerobic bottles (Becton Dickinson), flagged positive (aerobic bottles) after 6 days of incubation for small Gram-negative coccobacilli. After subculturing, small colonies were noted on chocolate agar after 48 h of incubation at 37 °C in the presence of 5 % CO₂. No growth was observed on sheep blood agar or on MacConkey agar. The organism was positive for oxidase, and negative for catalase and urease reactions. Tests for X and V growth factors were done with factor-containing paper discs (Becton Dickinson) placed on inoculated trypticase soy agar. The organism was factor V- but not factor X-dependent. Porphyrin test was used to confirm X factor-independent growth of the organism (Kilian, 2003). The isolate was identified as *Haemophilus paraphrophilus* by carbohydrate utilization and other biochemical reactions (API system NH; bioMérieux), according to the Albritton

Abbreviation: MRI, magnetic resonance imaging.

Fig. 1. Sagittal MRI scan of the cervical spine on hospital admission. (T1 fast spin echo technique) showing an abnormal signal intensity at the level of the C6–C7 vertebral bodies, with postgadolinium pathological enhancement of meninges from C4 to D1 and an anterior-paramedian epidural abscess, at the level of the C6–C7 intersomatic disc.

criteria (Albritton, 1982). This organism has been recently reclassified as *Aggregatibacter aphrophilus* (Norskov-Lauritsen & Kilian, 2006). The isolate was negative for β -lactamase and susceptible to ampicillin, cefotaxime, ceftriaxone, imipenem, ciprofloxacin, chloramphenicol and trimethoprim–sulfamethoxazole. After isolation of the infectious agent, we continued therapy with imipenem–cilastatin at the same dosage indicated above.

Additional studies were performed to determine any possible sources of bacteraemia. Radiographs of the chest and paranasal sinuses, a transthoracic echocardiogram and an abdominal ultrasound scan revealed no pathological findings. We also performed a dental X-ray that showed apical periodontal disease of the 27th tooth.

After 7 days of antibiotic treatment the fever completely disappeared and back pain was greatly reduced. The response to treatment was monitored with serial MRI, and measurement of erythrocyte sedimentation rate and C-reactive protein levels. After 12 weeks the erythrocyte sedimentation rate and C-reactive protein levels were normalized, the MRI scan showed significant improvement (Fig. 2), and antibiotic treatment with parenteral imipenem–cilastatin was stopped.

Discussion

We performed a MEDLINE search of the literature using the key words *H. paraphrophilus* cross-referenced with spondylodiscitis, discitis, spondylitis, vertebral osteomyelitis

Fig. 2. Sagittal MRI scan of the cervical spine after 12 weeks (T1 fast spin echo technique). The abnormal signal intensity has almost disappeared and the epidural abscess is no longer detectable.

and epidural abscess. *H. paraphrophilus*, first described by Zinnemann in 1968 (Zinnemann *et al.*, 1968), has been recently reclassified as *Aggregatibacter aphrophilus* (Norskov-Lauritsen & Kilian, 2006). It is an oral fastidious Gram-negative commensal bacterium with low pathogenicity (Liljemark *et al.*, 1984). Together with the other members of HACEK group (*Haemophilus aphrophilus*, reclassified as *Aggregatibacter aphrophilus* (Norskov-Lauritsen & Kilian, 2006); *Actinobacillus actinomycetemcomitans*, reclassified as *Aggregatibacter actinomycetemcomitans* (Norskov-Lauritsen & Kilian, 2006); *Cardiobacterium hominis*; *Eikenella corrodens*; *Kingella* spp.), it is an uncommon cause of human disease, but has been occasionally implicated in subacute endocarditis, osteomyelitis, brain and liver abscesses, and fatal pneumonitis (Le Gangneux *et al.*, 1993; Watkin *et al.*, 2003; Rabaud *et al.*, 1995; Jensen & Hojbjerg, 1985; Howard, 1981). Only 3 cases of spondylodiscitis and spinal abscess have been reported to date (Samuel *et al.*, 1997; Scerpella *et al.*, 1994; Wilson *et al.*, 1994), although the literature showed 15 cases of vertebral infection caused by *H. aphrophilus* (Colson *et al.*, 2001). The nature of this bacterium means that, in clinical specimens, it may remain undetected unless appropriate microbiological methods are used. In our case, blood culture bottles flagged positive after 6 days of incubation. This underlines that routine incubation of blood cultures for 5 days may not be adequate for recovering fastidious bacteria such as HACEK group members, for which it is recommended that cultures be held for 14 days.

Identification of *H. paraphrophilus* and its differentiation from *H. aphrophilus* or from *Aggregatibacter actinomycete-*

temcomitans may be difficult, due to the similarities in cell and colony morphology and growth requirements. The factor V-dependency of this isolate ruled out *H. aphrophilus*, which is factor V- and X-independent (Chadwick *et al.*, 1995), while the positive reaction for hydrolysis of *o*-nitrophenyl- β -D-galactoside ruled out *Aggregatibacter actinomycetemcomitans* (Dogan *et al.*, 1999). Due to its commensal nature, *H. paraphrophilus* may be identified as a simple contaminant, when isolated in the microbiology laboratory. Nevertheless, the pathogenic role of *H. paraphrophilus* in spondylodiscitis is further supported by recent data suggesting differentiation of *H. paraphrophilus* from *H. aphrophilus* is not founded on a genomic basis. In fact the two species have been recently reclassified as *Aggregatibacter aphrophilus*, *H. paraphrophilus* being considered a later heterotypic synonym of *H. aphrophilus* (Norskov-Lauritsen & Kilian, 2006). On the other hand, while *Staphylococcus aureus* is the most frequent causative agent of acute vertebral osteomyelitis in the young, Gram-negative bacilli and other pathogens, like *Brucella melitensis*, anaerobic bacteria, agents of actinomycosis or nocardiosis, mycobacteria, fungi or parasites (Soehle & Wallenfang, 2002), are frequently involved in the less active process characteristic of the adult. In our case, the repeated isolation of *Aggregatibacter aphrophilus* from a sterile site, the fact that no other micro-organism was isolated from the patient, and the history of recent dental procedures and periodontal disease points to its aetiopathogenic role.

Most patients with spondylodiscitis and spinal epidural abscess have one or more predisposing conditions, such as diabetes mellitus, alcoholism, infection with human immunodeficiency virus, spinal abnormality or a potential local or systemic source of infection, such as sinusitis, chronic lung disease, mitral valve prolapse, rheumatic heart disease (Soehle & Wallenfang, 2002), but there are reported cases in otherwise healthy people (Honan *et al.*, 1996), as in this case. In about half of the cases bacteria reach the vertebral body by haematogenous dissemination, and the process tends to affect the more mobile spinal segments, such as lumbar and lower cervical regions. Although it has a relatively avascular nature, the intervertebral disc also may be affected (Garcia & Grantham, 1960). In nearly half of the osteoarticular infections caused by *Aggregatibacter aphrophilus* a recent dental procedure was traced (Huang *et al.*, 2005). Our case of cervical spondylodiscitis had an haematogenous origin and the most likely source of infection was the teeth, as there was radiological evidence of periodontal disease.

The incidence of spondylodiscitis and epidural abscess has doubled in the past two decades, owing to an ageing population, an increasing use of spinal instrumentation and vascular access, and the spread of injection-drug use (Darouiche, 2006). Nevertheless, vertebral osteomyelitis remains a rare condition, which may appear with non-specific findings of back pain, fever, leukocytosis, or a high erythrocyte sedimentation rate or C-reactive protein level, and therefore, it is often misdiagnosed on presentation,

particularly in neurologically intact patients. Instead, more common infectious conditions, such as osteomyelitis, discitis, meningitis, urinary tract infection, sepsis and endocarditis, and non-infectious conditions (intervertebral-disc prolapse, degenerative joint disease, spinal tumour, demyelinating illness, transverse myelitis and spinal haematoma) are frequently diagnosed at the time of initial evaluation. A suspected diagnosis is made on the basis of clinical findings and supported by laboratory data and imaging studies, but can be confirmed by the isolation of the organism from bone drainage. Bacteraemia causing or arising from spinal epidural abscess is detected in about 60 % of patients. If blood cultures yield negative results, the causative organisms should be sought by biopsy (Darouiche, 2006). In our case the precise microbiological diagnosis, derived from blood cultures, negated the need for a biopsy and the potential risks of spreading the infection or causing neurological damage. The evaluation of cerebrospinal fluid revealed a high level of proteins, which is suggestive of parameningeal inflammation. This finding can be found in three-quarters of patients with spondylodiscitis whose cerebrospinal fluid is evaluated. Nevertheless, lumbar puncture is not recommended for diagnosis, because of the associated potential risk.

Despite advances in diagnostic techniques, spondylodiscitis remains a therapeutic challenge and often receives suboptimal treatment. Surgical drainage, together with systemic antibiotics, must be considered the treatment of choice. Nevertheless, a few retrospective studies have reported similar outcomes in patients who were treated with antibiotics alone. However, in these studies, patients receiving antibiotics alone had no or minimal neurological impairment or smaller abscesses. Antibiotic therapy must be guided by the results of blood cultures (as in our case) or a computerized tomography-guided aspiration of the abscess (Siddiq *et al.*, 2004).

In conclusion, in light of this current report, *Aggregatibacter aphrophilus* should be added to the list of causative pathogens of spondylodiscitis, especially for adult patients with a history of recent dental manipulation. Medical therapy may be the only treatment in patients who are neurologically intact, if the microbial cause is identified and the clinical condition is closely monitored.

References

- Albritton, W. L. (1982). Infections due to *Haemophilus* species other than *Haemophilus influenzae*. *Annu Rev Microbiol* **36**, 199–216.
- Chadwick, P. R., Malnick, H. & Ebizie, A. O. (1995). *Haemophilus paraphrophilus* infection: a pitfall in laboratory diagnosis. *J Infect* **30**, 67–69.
- Colson, P., La Scola, B. & Champsaur, P. (2001). Vertebral infections caused by *Haemophilus aphrophilus*: case report and review. *Clin Microbiol Infect* **7**, 107–113.
- Darouiche, R. O. (2006). Spinal epidural abscess. *N Engl J Med* **355**, 2012–2020.

- Dogan, B., Asikainen, S. & Jousimies-Somer, H. (1999). Evaluation of two commercial kits and arbitrarily primed PCR for identification and differentiation of *Actinobacillus actinomycetemcomitans*, *Haemophilus aphrophilus*, and *Haemophilus paraphrophilus*. *J Clin Microbiol* **37**, 742–747.
- Garcia, A., Jr & Grantham, S. A. (1960). Hematogenous pyogenic vertebral osteomyelitis. *J Bone Joint Surg Am* **42-A**, 429–436.
- Honan, M., White, G. W. & Eisenberg, G. M. (1996). Spontaneous infectious discitis in adults. *Am J Med* **100**, 85–89.
- Howard, J. (1981). Fatal pneumonitis associated with an ampicillin-resistant non- β -lactamase producing strain of *Haemophilus paraphrophilus*. *Can J Med Technol* **43**, 174–175.
- Huang, S.-T., Lee, H.-C., Lee, N.-Y., Liu, K.-H. & Ko, W.-C. (2005). Clinical characteristics of invasive *Haemophilus aphrophilus* infections. *J Microbiol Immunol Infect* **38**, 271–276.
- Jensen, K. T. & Hojbjerg, T. (1985). Meningitis and brain abscess due to *Haemophilus paraphrophilus*. *Eur J Clin Microbiol* **4**, 419–421.
- Kilian, M. (2003). *Haemophilus*. In *Manual of Clinical Microbiology*, 8th edn, pp. 623–635. Edited by P. R. Murray, E. J. Baron, J. H. Jorgensen, M. A. Tenover & R. H. Tenover. Washington, DC: American Society for Microbiology.
- Le Gangneux, E., Macro, M., Fournier, L., Malbrun, B. & Loyau, G. (1993). Osteitis of the pubis caused by *Haemophilus paraphrophilus*. *Rev Rhum Ed Fr* **60**, 631–632.
- Liljemark, W. F., Bloomquist, C. G., Uhl, L. A., Schaffer, E. M., Wolff, L. F., Pihlstrom, B. L. & Bandt, C. L. (1984). Distribution of oral *Haemophilus* species in dental plaque from a large adult population. *Infect Immun* **46**, 778–786.
- Norskov-Lauritsen, N. & Kilian, M. (2006). Reclassification of *Actinobacillus actinomycetemcomitans*, *Haemophilus aphrophilus*, *Haemophilus paraphrophilus* and *Haemophilus segnis* as *Aggregatibacter actinomycetemcomitans* gen. nov., comb. nov., *Aggregatibacter aphrophilus* comb. nov. and *Aggregatibacter segnis* comb. nov., and emended description of *Aggregatibacter aphrophilus* to include V factor-dependent and V factor-independent isolates. *Int J Syst Evol Microbiol* **56**, 2135–2146.
- Rabaud, C., May, T., Hoen, B., Lion, C. & Canton, P. (1995). Liver abscess caused by *Haemophilus paraphrophilus* and *Streptococcus anginosus*. *Ann Biol Clin (Paris)* **53**, 359–360.
- Samuel, W., Dryden, M., Sampson, M., Page, A. & Shepherd, H. (1997). Spinal abscess of *Haemophilus paraphrophilus*: a case report. *Spine* **22**, 2763–2765.
- Scerpella, E. G., Wu, S. & Oefinger, P. E. (1994). Case report of spinal epidural abscess caused by *Haemophilus paraphrophilus*. *J Clin Microbiol* **32**, 563–564.
- Siddiq, F., Chowfin, A., Tight, R., Sahmoun, A. E. & Smego, R. A., Jr (2004). Medical vs surgical management of spinal epidural abscess. *Arch Intern Med* **164**, 2409–2412.
- Soehle, M. & Wallenfang, T. (2002). Spinal epidural abscesses: clinical manifestations, prognostic factors, and outcomes. *Neurosurgery* **51**, 79–85.
- Watkin, R. W., Lang, S., Littler, W. A. & Elliott, T. S. (2003). *Haemophilus paraphrophilus* prosthetic valve endocarditis. *J Infect* **46**, 191–194.
- Wilson, C. M., Reiss-Levy, E. A., Sturgess, A. D. & Au, T. C. (1994). *Haemophilus paraphrophilus* vertebral osteomyelitis. *Med J Aust* **160**, 512–514.
- Zinnemann, K., Rogers, K. B., Frazer, J. & Boyce, J. M. (1968). A new V-dependent *Haemophilus* species preferring increased CO₂ tension for growth and named *Haemophilus paraphrophilus*, nov. sp. *J Pathol Bacteriol* **96**, 413–419.