CASE REPORTS

Fatal case of sepsis caused by a non-haemolytic strain of *Streptococcus pyogenes*

The β -haemolytic phenotype of *Streptococcus pyogenes* on blood media, which is due to the liberation of streptolysin S, is critical to the recognition of this pathogen in the diagnostic laboratory. We report the isolation of a non-haemolytic variant of *S pyogenes* from a blood culture that was taken from a patient who died of sepsis. Non-haemolytic isolates of *S pyogenes* are uncommon, very rarely associated with bacteraemia or sepsis, and may be difficult to recognise, especially if isolated from non-sterile sites.

Case report

A morbidly obese woman in her 80s was admitted with a 1-week history of a productive cough and breathlessness. Her past history included type II diabetes mellitus, hypertension and chronic leg ulcers. On examination, she was pyrexial (39°C), pulse was 120/min and respiratory rate 26/min. Blood pressure was 95/45 mm Hg. There was no evidence of cellulitis, and no murmurs were detected. A chest radiograph revealed left ventricular failure; no consolidation was evident, although the basal lung fields were poorly visualised. She had a haemoglobin of 10.8 g/dl and a total white blood cell count of $17 \times 10^9/l$ (95% polymorphonuclear cells). C-reactive protein was 198 mg/l. She was treated with intravenous co-amoxiclav for presumed lower respiratory tract infection and sepsis, but died on the day of admission.

Blood cultures (one aerobic and one anaerobic bottle) signalled positive on a Bactec 9240 instrument after 1 day of incubation and Gram-positive cocci in chains were seen in the Gram film. The following day, cream, non-mucoid, non-haemolytic, catalase-negative colonies grew on horse blood agar (Oxoid) incubated aerobically and anaerobically. The colonies became large (3–4 mm in diameter) with a crenated edge and a depressed central ring after 48 h incubation, but remained non-haemolytic (fig 1). Only minimal α -haemolysis was observed around densely grouped colonies. The isolate was sensitive to bacitracin, L-pyrrolidonyl- β -naphthylamide and DNase positive and possessed only the Lancefield group A antigen (Prolex Streptococcal Grouping Latex kit; Pro-Lab Diagnostics, Neston, UK). Identification using both the Vitek 2 and the API Strep systems confirmed the isolate to be *S pyogenes*. The isolate was sensitive to penicillin, erythromycin and tetracycline using the British Society for Antimicrobial Chemotherapy (BSAC) disk testing methodology. The non-haemolytic phenotype remained stable on repeated subculture. The isolate was typed as *emm*-type 28, T-type 28, opacity factor positive (Laboratory of HealthCare Associated Infection, Centre for Infections, Health Protection Agency, Colindale, London).

Discussion

S pyogenes typically produces β -haemolytic colonies on blood agar, and some strains are well-recognised to produce mucoid colonies.

Figure 1 Colonies of non-haemolytic *Streptococcus pyogenes* incubated on horse blood agar for 48 h. Aerobic and anaerobic cultures were identical in appearance.

Non-mucoid, non-haemolytic variants of *S pyogenes* have been recognised previously,¹ but have rarely been reported from blood cultures.^{2–4} The β -haemolytic phenotype is due to the liberation of streptolysin S. Strains that only produce streptolysin O do not exhibit typical β -haemolysis on traditional blood media. Furthermore, streptolysin S isogenic mutants of *S pyogenes* have been shown to be markedly less virulent in a murine model of infection.⁵ This may, at least in part, explain the apparent rarity of invasive infections caused by non-haemolytic isolates of *S pyogenes*. Of the four cases of bacteraemia previously reported, three were elderly patients, including one fatal case of pneumonia,² and one was a 7-year-old child.³ In the latter case, a throat swab from the child had initially yielded a false-negative result. The two cases of bacteraemia previously reported in the UK were due to an infrequently encountered *emm*-type 58 *S pyogenes*.⁴

Non-haemolytic variants of *S pyogenes* may be difficult to recognise when isolated on blood media.^{3,4,6} In the present case, the isolate was obtained in pure growth from a blood culture, and consequently was formally identified. Had the isolate been obtained in mixed culture or from a non-sterile site such as the nasopharynx, the non-haemolytic appearance may have led to the organism being dismissed as a contaminant or as commensal flora without further identification. Clinical microbiologists and biomedical scientists should be alert to the possibility of non-haemolytic variants of *S pyogenes* from both sterile and non-sterile sites.

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David P J Turner, Sarah I Gunn

Department of Clinical Microbiology, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK

Correspondence to: Dr David P J Turner, Department of Clinical Microbiology, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham NG7 2UH, UK; david.turner@nottingham.ac.uk

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References

- 1 Colebrooke L, Elliott SD, Maxted WR, Morley CW, Mortell M. Non-haemolytic group-A streptococci. *Lancet* 1942;ii:30–1.
- 2 Taylor MB, Barkham T. Fatal case of pneumonia caused by a nonhemolytic strain of *Streptococcus pyogenes*. *J Clin Microbiol* 2002;40:2311–12.
- 3 Cimolai N, Trombley C, Bhanju NM. Nonhemolytic *Streptococcus pyogenes* causing invasive infection. *Clin Pediatr (Phila)* 2002;41:453.
- 4 Weightman NC, Barnham MR. Report of unusual clinical appearance in bacteraemia with nonhaemolytic M-type 58 *Streptococcus pyogenes*. *Indian J Med Res* 2004;119:17–21.
- 5 Betschel SD, Borgia SM, Barg NL, et al. Reduced virulence of group A streptococcal Tn916 mutants that do not produce streptolysin S. *Infect Immun* 1998;66:1671–9.
- 6 Dierksen KP, Tagg JR. Haemolysin-deficient variants of *Streptococcus pyogenes* and *S. dysgalactiae* subsp. *equisimilis* may be overlooked as aetiological agents of pharyngitis. *J Med Microbiol* 2000;49:811–16.

Rare co-existence of multifocal myoepitheliosis with infiltrating ductal carcinoma of the breast

Lesions composed of myoepithelial cells are known to occur in salivary gland, but they are uncommon in the breast.¹ These range from benign lesions, such as myoepithelioma, to malignancies, such as adenoid cystic carcinoma and myoepithelial carcinoma. The predominance myoepithelial cells mainly in the terminal duct-lobular units (TDLUs) with formation of multifocal lesions is termed myoepitheliosis.² In the breast, this condition has been reported previously with other benign lesions such as sclerosing adenosis.

Recently, a role for myoepithelial cells in the pathogenesis of carcinoma has also been suggested. There are no previous reports describing the occurrence of myoepitheliosis with breast carcinoma. This report describes a unique case of dual occurrence of myoepitheliosis with infiltrating ductal carcinoma (IDC). We hope that future studies will disclose the relationship, if any, between the two lesions.

Case report

A 40-year-old woman presented to the surgical outpatient department with a lump in the left breast for the last 6 months. On examination, a hard mass was seen in the central part. A mammographic examination showed it to be a high-density lesion with foci of microcalcification. Fine-needle aspiration cytology from the mass showed the presence of an IDC. A left-sided modified radical mastectomy with axillary clearance was performed subsequently, and the specimen was sent for histopathological examination.

Pathological findings

Grossly, the specimen comprised left breast with overlying elliptical skin flap bearing the nipple, areola and axillary tail. Serial slicing showed two nodules—the larger one located centrally, measuring 6×4×4 cm, and the smaller one located in the left upper quadrant, measuring 2×1×1 cm. The larger nodule was situated close to the deep resection plane (0.2 cm), but the skin, nipple and areola were free. Adequate sections were taken from both nodules for microscopy and all the axillary lymph nodes were sampled.

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Figure 1 A focus of myoepitheliosis showing proliferation of cuboidal to spindle-shaped myoepithelial cells leading to the formation of a nodule.

The larger nodule showed an IDC, grade II, on microscopy (Elston and Ellis modification of Bloom Richardson classification).³ The tumour extended close to the deep resection plane; however, it was free. The smaller nodule showed multiple foci of proliferating oval to spindle cells, involving almost all the TDLUs as well as the surrounding areas (figs 1 and 2). Similar foci were also identified in the sections taken from peritumoural (fig 3) and tumour-free areas. The intervening stroma showed fibrosis. No atypia or mitosis was noted. The myoepithelial nature of these cells was confirmed by smooth muscle actin (SMA) and S-100 immunostaining. There was no evidence of any malignant change in the epithelial component in this nodule. Considering the above features, a diagnosis of IDC with multifocal myoepitheliosis was made. The lymph nodes from the axillary tail were free of tumour.

Discussion

Myoepithelial lesions of the breast range from the myoepithelial proliferations accompanying benign lesions—for example, sclerosing adenosis, ductal hyperplasia and nipple adenoma—to malignancies such as adenoid cystic carcinoma, adenomyoepithelioma and myoepithelial carcinoma. Myoepitheliosis is a benign condition characterised by multifocal proliferation of spindle to cuboidal myoepithelial cells generally located in the TDLUs. It can occur in two forms: the intraductal form, in which there is variable distention and occlusion of the TDLUs, and periductal form, which is often associated with sclerosis. The periductal variety, now considered a variant of

Figure 3 High-power photomicrograph showing the proliferating oval to spindle myoepithelial cells.

sclerosing adenosis, may sometimes be misdiagnosed as an invasive carcinoma, particularly in the background of atrophy.² The present case highlights a mixed pattern with both intraductal and periductal components. Myoepitheliosis generally does not present as a mass lesion. However, if myoepithelial cells form aggregates, it may sometimes be felt as a nodule, as was seen in our case.² Immunohistochemically, the cells exhibit positivity for protein markers such as SMA and S-100 protein.⁴ The recently described nuclear protein p63 is also considered to be sensitive and specific for identification of myoepithelial cells.⁵ Our case showed positivity for SMA as well as S-100 protein, but the intensity of staining was stronger for SMA. Tavassoli² described three patients with myoepitheliosis in a series of myoepithelial lesions of the breast. None of her patients, however, had a coexisting IDC.

The exact contribution of myoepithelial cell proliferation to ductal carcinomas is unclear. Several reports suggest that 2–18% of the IDC show focal or diffuse myoepithelial differentiation by immunohistochemical protein markers (eg, basal cytokeratins, actin, calponin, caldesmon and S-100 protein). Experimental studies have shown a considerable overlap between the genetics of lesions arising from myoepithelial and epithelial cells, and it has been suggested that the two cell types are derived from the same precursor.⁶ Also, the myoepithelial cells have been shown to secrete a variety of tumour-suppressor molecules, such as maspin, laminin-1 and Wilms' tumour-1, which are thought to have anti-invasive and anti-angiogenic effects on carcinoma and precancer cells. The loss of these molecules due to myoepithelial cell injury may lead to cell proliferation, angiogenesis and invasion.^{7,8} Excision is the treatment of choice in myoepitheliosis. However, in the present case, the future course of treatment and outcome depend on the coexistent malignancy.²

To conclude, we document the presence of a rare multifocal myoepitheliosis in a case of IDC. However, the link between the two lesions in the same breast cannot be explained from this single case report. Future studies are needed to establish the exact role of such proliferations of myoepithelial cells in breast malignancies.

Alka Bhatia, Ashim Das, Yashwant Kumar
Department of Histopathology, Chandigarh, India

Correspondence to: A Das, Department of Pathology, PGIMER, Chandigarh, India-160012; asim126@gmail.com

References

- 1 Sciubba JJ, Brannon RB. Myoepithelioma of salivary glands: report of 23 cases. *Cancer* 1982;49:562–72.
- 2 Tavassoli FA. Myoepithelial lesions of the breast. Myoepitheliosis, adenomyoepithelioma and myoepithelial carcinoma. *Am J Surg Pathol* 1991;15:554–68.
- 3 Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. The value of histological grades in breast cancer. Experience from a large study with long term follow up. *Histopathology* 1991;19:403–10.
- 4 Sebastian L, Margit GK, Andrea S, et al. Metaplastic breast carcinomas: are they of myoepithelial differentiation? Immunohistochemical profile of the sarcomatoid subtype using novel myoepithelial markers. *Am J Surg Pathol* 2005;29:347–53.
- 5 Batistatou A, Stefanou D, Arkoumani E, et al. The usefulness of p63 as a marker of breast myoepithelial cells. *In Vivo* 2003;17:573–6.
- 6 Lakhani SR, Hare MUO. The mammary myoepithelial cell—Cinderella or ugly sister? *Breast Cancer Res* 2001;3:1–4.
- 7 Man YG, Tai L, Barner R, et al. Cell clusters overlying focally disrupted mammary myoepithelial cell layers and adjacent cells in the same duct display different immunohistochemical and genetic features: implications for tumor progression and invasion. *Breast Cancer Res* 2003;5:231–41.
- 8 Gudjonsson T, Ronnov-Jessen L, Villadsen R, et al. Normal and tumor-derived myoepithelial cells differ in their ability to interact with luminal breast epithelial cells for polarity and basement membrane deposition. *J Cell Sci* 2002;115:39–50.

Primary hyperparathyroidism and metastatic carcinoma within parathyroid gland

Involvement of the parathyroid glands by metastatic tumour is rare. In autopsy studies of known cancer patients, it was noted in 0.2–11.9% of individuals.¹ Hypoparathyroidism and hypocalcaemia as a result of parathyroid destruction by tumour is unusual.^{2,3} We report a case of hyperparathyroidism due to parathyroid hyperplasia with simultaneous occurrence of metastatic bronchogenic adenocarcinoma to a parathyroid gland.

Case report

A 75-year-old woman was referred with hypercalcaemia. Six months earlier she had presented to an osteoporosis clinic with generalised pain in the upper limbs. She reported anorexia and mild weight loss but was otherwise asymptomatic. Specifically there were no respiratory symptoms. A bone density scan revealed osteoporosis. Routine biochemical investigations revealed hypercalcaemia, raised parathyroid hormone level and normal renal function (table 1). A parathyroid pertechnetate/MIBI subtraction scan suggested the presence of an enlarged left superior parathyroid gland. The patient was a non-smoker and had no significant past medical history. Plain radiographs of the chest and renal tracts taken 6 months prior to surgery were normal. A diagnosis of primary hyperparathyroidism seemed secure and surgical exploration advised. Prior to operation a hard palpable lymph node in the right submandibular region

Figure 2 Infiltrating ductal carcinoma (broad arrow) with a focus of myoepitheliosis in the adjoining breast (arrow).