The Journal of Laryngology and Otology
February 1992, Vol. **106,** pp. 173–177

Prediagnostic malakoplakia presenting as a chronic inflammatory mass in the soft tissues of the neck

A. G. Douglas-Jones, C. Rodd, E. M. V. James, R. G. S. Mills (Cardiff)

Abstract
Malakoplakia presenting in the head and neck is very rare. We present a case of an inflammatory mass in the neck, clinically mimicking actinomycosis in a 67-year-old man. Repeated culture of *E. coli* and histological and electron microscopic examination of biopsy material showed an infiltration of granular macrophages and intracellular gram negative bacilli, but no classical Michaelis-Gutmann bodies. The clinical and pathological findings and criteria for the diagnosis of malakoplakia are discussed.

Introduction

Malakoplakia is a rare form of chronic inflammatory response which is characterized by an infiltrate of lymphocytes, plasma cells and conspicuous large granular macrophages (Von Hansemann cells) classically associated with laminated calcified bodies, the so-called Michaelis-Gutmann bodies. Although most commonly encountered in the genito-urinary tract, particularly the urinary bladder, malakoplakia has been described in numerous other sites, usually as individual case reports, comprehensively reviewed by McClure (1983). Involvement of sites in the ear, nose and throat are rare but malakoplakia in the middle ear, (Azadeh and Ardehali, 1983), temporal bone (Nayar *et al.*, 1991), tonsil (Kalfayan and Seager, 1982), parotid gland (Dale and Robinson, 1988), tongue (Love *et al.*, 1985), larynx (Gabrielides *et al.*, 1981) and maxillary antrum (Nistal *et al.*, 1985) have been reported. Only one case is previously described in the soft tissues of the neck, in which malakoplakia was associated with an underlying carcinoma of the nasopharynx (McCormick and Timme, 1982). The case described here presented clinically as a chronic inflammatory mass in the neck unassociated with other pathology mimicking actinomycosis. Biopsies to establish a tissue diagnosis were initially non-specific and culture of wound exudate and biopsy material grew *E. coli*. An important objective during investigation was the exclusion of an underlying malignant neoplasm. Thorough examination under general anaesthesia and extensive local debridement of inflamed tissue allowed definitive tissue diagnosis. Appropriate antibiotic therapy subsequently effected resolution.

Case report

A 67-year-old Caucasian male presented with a four-week history of a painless but progressive swelling in the left submandibular region. He had noted some anorexia and lethargy but was otherwise symptom-free with no history of obvious pyrexia. There was no significant past medical history. The mass had initially been treated by his General Practitioner with a course of cefuroxime to no effect.

Clinical examination revealed a 10 × 15 cm swelling in the left submandibular region extending on to the angle of the mandible. The mass was of firm consistency, indurated and non-tender. The overlying skin was erythematous but not ulcerated examination of the ENT system otherwise revealed no abnormality and excluded any associated primary pathology.

A clinical diagnosis of actinomycosis was made with a possible differential diagnosis of lymphoma or tuberculosis and a Tru-cut biopsy performed to obtain material for histopathological and bacteriological diagnosis. The Tru-cut biopsy contained skin and connective tissue only and repeat biopsy was recommended. Treatment with benzylpenicillin was commenced.

Rapid breakdown of the puncture wound at the site of the Tru-cut biopsy was followed by discharge of clear yellow serous fluid (Fig. 1). Full blood count and differential was normal. Bacterial culture from the wound showed a moderate growth of coliforms with a light growth of *Staph. epidermidis* but was negative for actinomycosis. Augmentin 1.2 g daily was substituted for the benzylpenicillin. Over the course of some four weeks antibacterial chemotherapy was maintained and numerous further local biopsies taken along with specimens for bacteriological study. *E. coli* sensitive to ampicillin was consistently grown but as material from an open wound site it was considered to be of questionable significance. The histopathology reports of both deep tissues and overlying epidermis revealed features of a non-specific chronic inflammation with a prominent foamy macrophage response. No granulomas, multinuclear giant cells, necrosis or vasculitis was found and special stains for bacteria, acid-fast bacilli, fungi, and parasites were all negative and there was no evidence of malignancy.

Clinically, the mass showed marginal reduction in size on continuing antibiotic therapy, but there was an accompanying relentless breakdown in the wounds at biopsy sites with persistent discharge. To exclude the remaining possibility of underlying neoplasm, in particular lymphoma, and to remove obvious deep necrotic material open exploration under general anaesthesia was undertaken. A deep cavitating lesion extending along the plane anterior to the upper sternocleido-mastoid muscle with surrounding dense induration and fibrous tissue was found. Necrotic and fibrotic muscle was excised. Multiple biopsies for both histological and bacterial examination was taken. The wound was packed with Acromycin gauze and left open to heal by granulation.

Examination of the ipsilateral tonsil carried out at the same time revealed fibrous induration. Pus, freely expressed from the crypts, also yielded a growth of *E. coli*. Tonsillar tissue biopsies were taken and the histopathological findings from these and the inflammatory neck mass are presented below.

The wound began healing in the immediate post-operative period. Repeated packing in the early stages was required, but by

From the Departments of ENT and Pathology, University Hospital of Wales, Heath Park, Cardiff CF4 4XN.
Accepted for publication: 24 October 1991

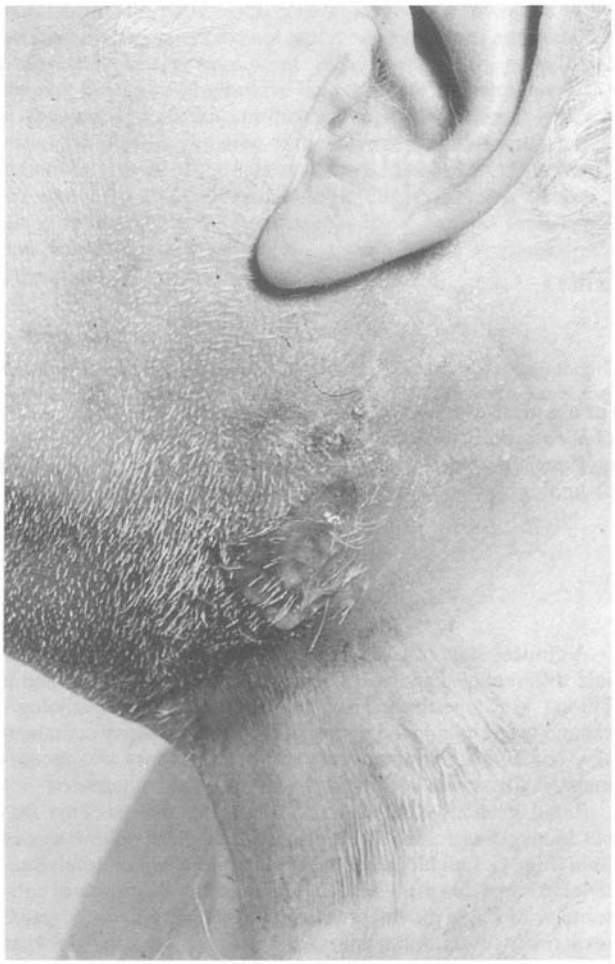

FIG. 1

Indurated mass in the left submandibular region showing wound breakdown with serous discharge.

two months healing by secondary intention was achieved. Antibiotic therapy (ampicillin) was maintained throughout the healing period.

Histological findings

Light microscopy

Dark brown tissue (1.7 × 1.1 × 0.5 cm) obtained at formal debridement showed sheets of large polygonal histiocytes with abundant finely granular eosinophilic cytoplasm and rounded regular central nuclei. Between the histiocytes there was an infiltrate of lymphocytes, plasma cells and neutrophil leucocytes, some of which appeared degenerate (Fig. 2). Sections were stained with periodic acid schiff (PAS) and Grocott for fungal elements, Wade Fite and Ziehl-Neelsen for mycobacteria, PAS with diastase pre-treatment, Von Kossa for calcium deposition, Perl's stain for iron. No organisms or Michaelis-Gutmann bodies containing calcium or iron were identified. The macrophage cytoplasm contained fine PAS-diastase resistant granules. Careful searching in the PAS stained sections revealed occasional rounded intracytoplasmic bodies (measuring 3–6 microns in diameter) which showed some evidence of lamination but no calcification (Fig. 3). In some haematoxylin and eosin stained sections, eosinophilic rod structures could be seen under oil immersion. Material from these areas was taken from the paraffin block, rehydrated, fixed in glutaraldehyde, post-fixed in 2 per cent osmium tetroxide and embedded in araldite resin. Semi-thin sections (1 micron) were stained with 0.5 per cent toluidene blue for screening for electron microscopy. In these thin toluidene blue stained sections groups of intracellular rod shaped structures could be clearly seen (Fig. 4). Ultrathin sections were placed on copper grids and stained with Uranyl actetate followed by lead citrate.

Electron microscopy

Ultrastructural examination showed poorly preserved tissue because of sub-optimal fixation. Numerous intracellular phagolysosomes could be seen, some of which contained degenerate bacilli. Numerous well preserved intracellular organisms were seen which had the cell wall morphology of gram negative bacilli (Fig. 5). The histological diagnosis was of chronic inflammation containing Gram negative bacilli with a predominant histocytic response.

Discussion

Our case illustrates difficulties in the recognition and management of an unusual cause of an inflammatory mass in the soft tissues of the neck occurring in association with *E coli*. The clinical presentation and initial course were characteristic of either a chronic specific infection, initially thought to be actinomycosis, or of an underlying malignancy, in particular lymphoma. However, repeated biopsies failed to identify a causative organism in support of a diagnosis of actinomycosis or any other specific chronic infective process and the histopathological picture of a non-specific chronic inflammatory response could not be taken as excluding the continuing possibility of an underlying neoplasm.

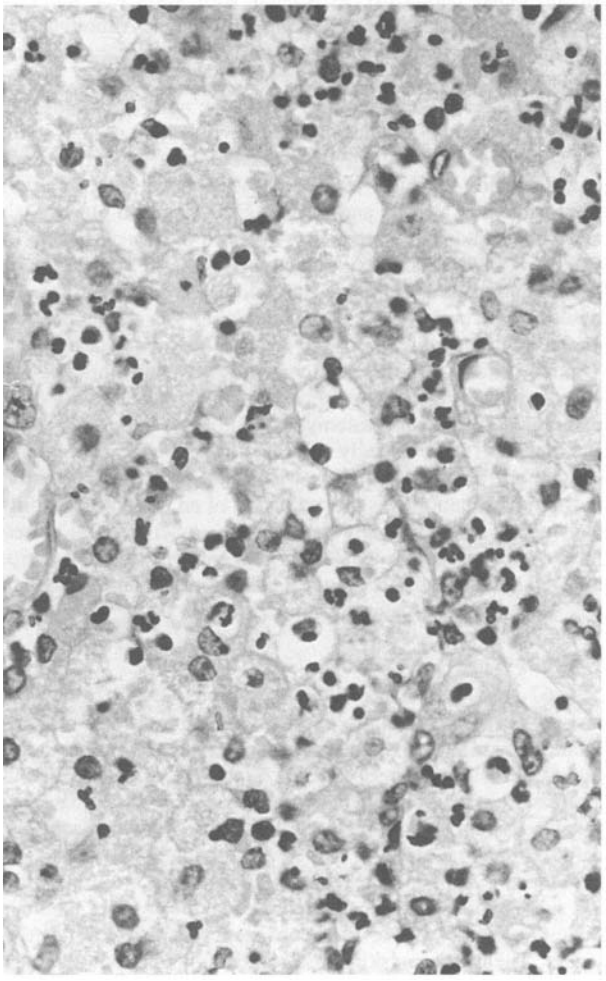

FIG. 2

Histology of open biopsy shows large histiocytes with granular cytoplasm with an infiltrate of lymphocytes, plasma cells and neutrophil leucocytes (Haematoxylin and eosin ×200)

https://doi.org/10.1017/S0022215100119012 Published online by Cambridge University Press

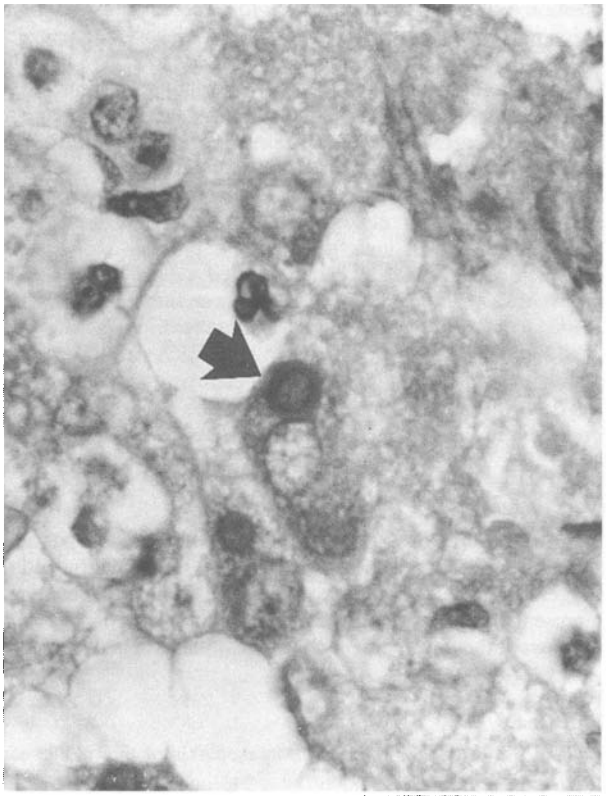

FIG. 3
Rounded laminated PAS positive intra cytoplasmic bodies (arrow) (PAS stain ×900)

Throughout the active phase of inflammation, bacterial cultures of wound discharge and tissue biopsies yielded light to heavy growths of coliform organisms sensitive to amoxycillin. Their significance as culture from an open wound was considered doubtful at the time, though in retrospect, they were clearly of relevance both in terms of the final histological findings and the response to prolonged apposite antibacterial therapy which, along with extensive surgical debridement, led to resolution and healing.

The nature and pathogenesis of malakoplakia are incompletely understood. Based on observations at the light microscopic level on 24 cases of malakoplakia of the urinary tract, Smith (1965) postulated that malakoplakia passed through three histological phases:

1. *Early prediagnostic* characterized by an infiltrate of plasma cells and macrophages of Von Hansemann morphology with focal infiltrates of eosinophils. No Michaelis-Gutmann bodies were seen in this stage.

2. *A classical phase* in which there were sheets of large macrophages with granular cytoplasm, with focal collections of lymphocytes and plasma cells and focal haemosiderin deposition, intracellular and intercellular calcospherules (Michaelis-Gutmann bodies) which contained calcium (von Kossa positive) and iron (Prussian blue positive) were seen.

3. *Fibrosing stage*. Peripheral and focal fibrosis separated the histiocytes and lymphocytes.

It is widely accepted that the diagnosis of malakoplakia should not be made in the absence of Michaelis-Gutmann bodies. However, it is also becoming apparent that there is a spectrum of histological changes characterized by an acute or chronic inflammatory response containing numerous large granular histocytic cells which may represent a tissue reaction which may evolve into classical malakoplakia over time. In the kidney, three chronic inflammatory responses occuring in the renal interstitium, megalocytic interstitial nephritis (MIN), xanthogranulomatous pyelonephritis (XPN), and renal parenchymal malakoplakia (RPM), while being separate morphological entities may represent a spectrum of unusual responses to microorganisms or their derivatives acting as immunogenic antigens (Ravel, 1967; Kelly and Murad, 1981). Experimentally, a lesion simulating malakoplakia (with Michaelis-Gutmann bodies) can be produced in the rat kidney by the injection of antigen derived from *E coli* cell walls. Interestingly, diluted antigen produces a lesion similar to megalocytic intestinal nephritis without classical Michaelis-Gutmann bodies supporting a postulated link between MIH and RPM (Garrett and McClure, 1982). A similar relationship has been postulated between histiocytic endometritis and endometrial malakoplakia (Buckley and Fox, 1980).

A unique case of retroperitoneal malakoplakia has been reported in which early biopsies showed acute inflammation, necrosis and granulation tissue where later biopsies showed reduced acute inflammatory cells but increased numbers of macrophages and lymphocytes (Colby, 1978).

Such a concept of a continuum of morphological changes in the development of malakoplakia is supported by studies at the ultrastructural level. The Von Hansemann cells are macrophages containing phagolysosomes, bacilliform organisms in various stages of degradation with amorphous aggregates and phospholipid membranes which become encrusted with calcium, phosphorus and iron (as determined by quantitative electron-probe x-ray analysis) (Sencer *et al.*, 1979) forming laminated Michaelis-Gutmann bodies (Lou and Teplitz, 1973; Lewin *et al.*, 1974).

The PAS positive diastase resistant granules seen in macrophages in malakoplakia at the light microscopic level are phagosomes at the ultrastructural level containing whorled

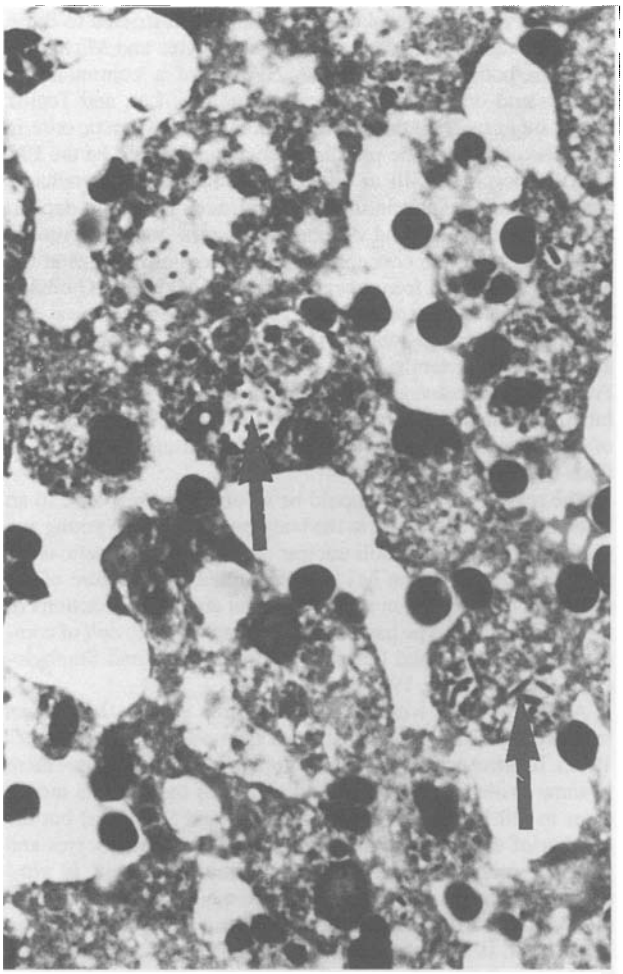

FIG. 4
Thin araldite embedded toluidine blue stained section showing groups of intracellular bacilli (arrows) (×625)

https://doi.org/10.1017/S0022215100119012 Published online by Cambridge University Press

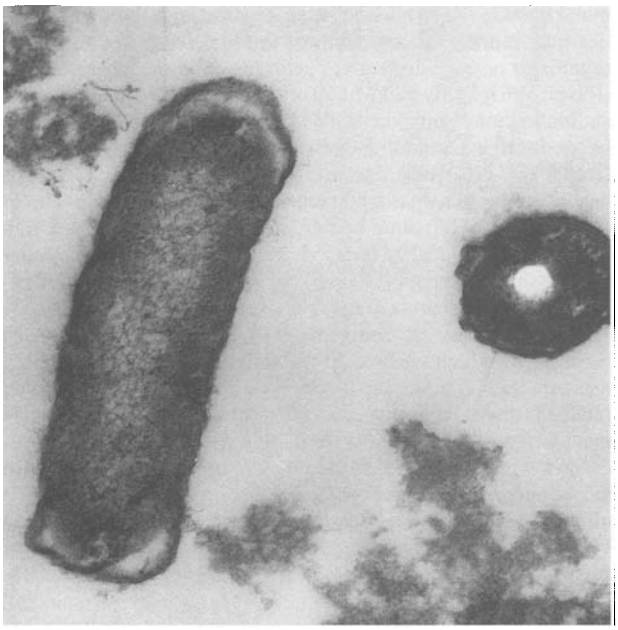

FIG. 5

Electron micrograph of an intracellular bacillus showing Gram negative cell wall morphology (×46000)

fingerprint-like myelin figures which are non-specific degradation products of cell membranes. Rywlin *et al.* (1969) proposed that the term malakoplakia should be restricted to those lesions containing the characteristic histiocytes and Michaelis-Gutmann bodies. Based on the concept of a continuum of changes and on their ultrastructural findings, Lou and Teplitz (1974) suggested that the earliest pathological diagnostic criteria for malakoplakia in the pre-diagnostic stage should be the EM identification of bacilli or bacillary remnants in macrophagic phagolysomal inclusions showing evidence of calcium deposition although whole and degenerate bacteria may be present. While accepting the concept of a continuum of changes at the ultrastructural level from phagolysomes to Michaelis-Gutmann bodies, some authors do not believe that the ultrastructural evidence proves that the matrix of the Michaelis-Gutmann body is always derived from bacterial products (McClure *et al.*, 1981). Protected from conventional antibiotics, it appears that intracellular *E. coli* in malakoplakia of the bladder can act as a reservoir of organisms resulting in persistent and recurrent urinary infections (Qualman *et al.*, 1984).

The reason why there should be an abnormal response to an infective agent at one site in the body, sometimes at a young age (Nayar *et al.*, 1991), is still unclear (no familial or genetic component to the condition has been identified). The nature of the organism does not seem to be important and tissue reactions of the malakoplakia type have been associated with *E. coli* of common serotypes 02 and 050 and with Klebsiella and Staphylococci (Sencer *et al.*, 1979).

A few patients without other systemic disease have been reported with malakoplakia at more than one site (Gupta *et al.*, 1972). In other patients with malakoplakia at multiple sites there is some evidence of an impaired ability of the patients monocytes to kill ingested organisms (*E. coli* and *S. aureus*) but the number of organisms phagocytosed by normal monocytes and patients' monocytes were not significantly different *in vitro* (Schreiber and Maderazo, 1978). In some cases of widespread malakoplakia there has been a concomitant malignancy, (Lewin *et al.*, 1974, 1976), tuberculosis or steroid therapy (Colby, 1978).

The possibility of an acquired immunodeficiency has been suggested but the localized nature of the disease argues against this concept. An acquired defect in digestion of phagocytozed material has been proposed, possibly due to impaired acidification of the lysosome secondary to carbonic anhydrase inhibition related to some drugs (sulphonamides, benzothiadiazides and acetozolamide) (Thorning and Vracko, 1975).

No differences in the ability of polymorphonuclear leucocytes to kill Gram negative or Gram positive bacteria was found between patients with malakoplakia and control subjects (Lewin *et al.*, 1976).

The pathogenesis of malakoplakia remains unknown but there appears to be an accumulation of numerous phagolysosomes in macrophages which undergo fusion to produce increasingly large structures which eventually calcify. This accumulation may represent antigenic overload during an infection or may be related to a defect or exocytosis or failure to discharge accumulated lysosomal debris. Corticosteroids, which stabilize lysosomal membranes could theoretically potentiate such a problem.

There was no evidence that any of the above factors was important in the pathogenesis in the case reported here.

Conclusion

We report this case to alert clinicians to this rare and possibly sometimes unrecognized cause of chronic inflammation and to suggest that the particular pathological findings encountered represent phases in a continuum of morphological changes leading toward the development of classical malakoplakia.

References

Azabeh, B., Ardehali, S. (1983) Malakoplakia of the middle ear. *Histopathology*, **7:** 129–134.

Buckley, C. H., Fox, H. (1980) Histiocytic endometritis. *Histopathology*, **4:** 105–109.

Colby, T. V. (1978) Malakoplakia. Two unusual cases which presented diagnostic problems. *American Journal of Surgical Pathology*, **2:** 377–381.

Dale, J. C., Robinson, R. A. (1988) Malakoplakia of the parotid gland. *Journal of Laryngology and Otology*, **102:** 737–740.

Gabrielides, G. G., Schimer, F., Schwartz, S. (1981) Malakoplakia of the larynx. *Pathology, Research and Practice*, **172:** 53–57.

Garrett, I. R., McClure, J. (1982) Renal malakoplakia. Experimental production and evidence of a link with interstitial megalocytic nephritis. *Journal of Pathology*, **136:** 111–122.

Gupta, R. K., Schuster, R. A., Christian, W. D. (1972) Autopsy findings in a unique case of malakoplakia. A cytoimmunohistochemical study of Michaelis-Gutmann bodies. *Archives of Pathology*, **93:** 42–54.

Kalfayan, B., Seager, G. M. (1982) Malakoplakia of the palatine tonsil. *American Journal of Clinical Pathology*, **78:** 390–394.

Kelly, D. R., Murad, T. M. (1981) Megalocytic interstitial nephritis, xanthogranulomatous pyelonephritis and malakoplakia. *American Journal of Clinical Pathology*, **75:** 333–344.

Lewin, K. J., Harell, G. S., Lee, A. S., Crowley, L. G. (1974) Malakoplakia. An electron microscopic study: demonstration of bacilliform organisms in malakoplakic macrophages. *Gastroenterology*, **66:** 28–45.

Lewin, K. J., Fair, W. R., Steigbigel, R. T., Winberg, C. D., Droller, M. J. (1976) Clinical and laboratory studies into the pathogenesis of malakoplakia. *Journal of Clinical Pathology*, **29:** 354–363.

Lou, T. Y., Teplitz, C. (1973) Ultrastructural morphogenesis of malakoplakia and so-called Michaelis-Gutmann bodies. *Laboratory Investigation*, **28:** 390–395.

Lou, T. Y., Teplitz, C. (1974) Malakoplakia, pathogenesis and ultrastructural morphogenesis: a problem of altered macrophage (phagolysosomal) response. *Human Pathology*, **5:** 191–195.

Love, B. B., Stanford, H. S., Jones, B. (1985) Malakoplakia of the tongue base. A case report. *Journal of Otolaryngology*, **14(3):** 179–182.

McClure, J. (1983) Malakoplakia. *Journal of pathology*, **140:** 275–330.

McClure, J., Cameron, C. H. S., Garrett, R. G. (1981) The ultrastructural features of malakoplakia. *Journal of Pathology*, **134:** 13–25.

McCormick, K., Timme, A. H. (1982) Malakoplakia of the nasopharynx associated with carcinoma. *Journal of Laryngology and Otology*, **96:** 737–742.

Nayar, R. C., Garg, I., Alapatt, J. J. (1991) Malakoplakia of the tem-

poral bone in a nine-month-old infant. *Journal of laryngology and Otology,* **105:** 568–570.
Nistal, M., Regadera, J., Razquin, S., Paniagua, R., Gavilan, J. (1985) Malakoplakia of the maxillary sinus. *Annals of Otology, Rhinology and Laryngology,* **94:** 117–120.
Qualman, S. J., Gupta, P. K., Mendelsohn, G. (1984) Intracellular escerichia coli in urinary Malakoplakia: a reservoir of infection and its therapeutic implications. *American Journal of Clinical Pathology,* **81:** 35–42.
Ravel, R. (1967) Megalocytic interstitial nephritis. An entity probably related to Malakoplakia. *American Journal of Clinical Pathology,* **47:** 781–789.
Rywlin, A. M., Ravel, R., Hurwitz, A. (1969) Malakoplakia of the colon. *American Journal of Digestive diseases,* **14:** 491–499.
Schreiber, A. G., Maderazo, E. G. (1978) Leucocyte function in Malakoplakia. *Archives of Pathology and Laboratory Medicine,* **102:** 534–537.
Sencer, O., Sencer, H., Uluoglu, O., Torunoglu, M., Tatlicioglu, E (1979) Malakoplakia of the skin. Ultrastructure and quantitative X-ray microanalysis of Michaelis-Gutmann bodies. *Archives of Pathology and Laboratory Medicine,* **103:** 446–450.
Smith, B. H. (1965) Malakoplakia of the urinary tract. *American Journal of Clinical Pathology,* **43:** 409–417.
Thorning, D., Vracko, R. (1975) Malakoplakia. Defect in digestion of phagocytosed material due to impaired vacuolar acidification. *Archives of Pathology,* **99:** 456–460.

Address for correspondence:
Dr A. G. Douglas-Jones,
Pathology Department,
University Hospital of Wales,
Heath Park,
Cardiff,
South Glamorgan CF4 4XN.

Key words: Malacoplakia; Neck