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Prognostic markers of pleomorphic xanthoastrocytoma

Sir: Leonard *et al*. report a childhood example of pleomorphic xanthoastrocytoma (PXA) undergoing anaplastic change with meningeal dissemination.[1] The authors take advantage of an unprecedented casuistic setting to comment on the more general issue of prognostic standards of PXAs. The potential of proliferation markers to predict outcome is specifically addressed, and the authors observe that, except for case studies 'there is no data available on indices of cellular proliferation in PXAs'.

We recently surveyed a series of eight PXAs in terms of MIB1 immunostaining.[2] Five tumours morphologically corresponding to classical PXA had an average labelling index of 2.05%, while three cases with signs of anaplasia (including necrosis in two) featured a mean of 4.66% MIB1 positive nuclei. There was no tumour-related mortality in either group during an average 6.7-year follow-up, and only one patient experienced recurrence 10 years after resection of an anaplastic tumour. The other two cases with histologically higher-grade PXAs were free of disease at 1 year and 5 year of follow-up, respectively.

Remarkably, while classical PXAs were comparable to common fibrillary astrocytomas with respect to proliferation, the histologically malignant lesions had ostensibly lower labelling indices than their ordinary counterparts, especially glioblastoma multiforme (GBM).[3] One interpretation of these results might possibly relate to a less aggressive intrinsic behaviour of some PXAs. Indeed, there has been a general perception, substantiated by a recent comprehensive review of necrotic PXAs, that such neoplasms may on occasion pursue a less aggressive course.[4]

We certainly share the opinion of Leonard *et al*.[1] on necrosis being a hallmark of unfavourable outcome in PXAs. However, contrarily to their view that 'cases with necrotic areas [are] incompatible with a diagnosis of PXA' we favour instead the argument that any PXA with necrosis not necessarily be equated to GBM.[4] While GBM most likely represents a point of convergence in the malignant evolution of PXAs, recent molecular evidence suggests that an important subset of histologically malignant PXAs actually fall short of genetic criteria identifying the former tumours. Specifically, amplification of the epidermal growth factor receptor and allelic losses on chromosomes 10q and 19q, while pivotal during astrocytoma progression, were distinctly rare in eight cases of low and high-grade PXAs analysed by Paulus *et al*.[5] Also, reports of cases involving a dual astrocytic/neuronal commitment of tumour cells raise the possibility of at least a subset of PXAs being akin to so-called 'desmoplastic supratentorial neuroepithelial tumours', a group of usually low-grade pluripotent neoplasms, rather than purely glial in origin.[6,7] Therefore, while the contribution of a genuine astrocytic component to both the phenotype and behaviour of PXAs is unquestionable, the biological scenario of their progression may not parallel that underlying ordinary astrocytomas.

In other words, the cellular target of oncogenic transformation giving rise to PXA, its malignant potential, as well as the timing of critical switches in its cell-cycle have not yet been satisfactorily identified. As a consequence, diagnostic attempts to assess the behaviour of these tumours, whether by analogy with ordinary astrocytomas or inference from proliferation kinetics, unwittingly disregard—while remaining contingent upon—some conceptual problems.

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Thrombomodulin immunostaining and ductal carcinoma of the prostate

Sir: In a recent article, Ordonez describes the use of

thrombomodulin immunostaining in the diagnosis of transitional cell carcinoma.[1]

Papillary tumours involving the prostate fall into two main categories, either ductal carcinoma of the prostate or transitional cell carcinoma of the urothelium. In all but two of the ductal carcinomas described in the literature immunostaining for prostate specific antigen (PSA) has been positive.[2] We recently reviewed one of the cases reported as PSA negative,[3] and found this papillary tumour to be CEA positive, PSA and prostatic acid phosphatase (PAP) negative. Our next step was to use thrombomodulin in this case and the series of 12 ductal carcinomas we reported. All the cases were negative.

We conclude that thrombomodulin may be of use in diagnosing ductal carcinoma of the prostate when immunostaining for PSA and PAP is negative.

We thank Dr N L Reeve for allowing us to review the case.

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Anaplastic gastric adenocarcinoma with extensive neutrophilic infiltration

Sir: In relation to the paper on anaplastic large cell lymphoma with extensive polymorph and eosinophil infiltration by McCluggage *et al.*,[1] we wish to draw attention to an interesting histological variant of gastric adenocarcinoma which shows a similar, heavy, acute inflammatory infiltrate and cytological anaplasia.

In a series of 120 gastrectomies for carcinoma from two district general hospitals in South Wales, five tumours consisted of sheets of highly pleomorphic, poorly cohesive, malignant cells intermingled with large numbers of polymorphs (Figure 1). All five were advanced tumours (T2N0 to T2N2) arising in elderly patients (64–79 years), with nodal metastases in four cases.

In all cases, the tumours arose on a background of chronic gastritis. Two were proximal, two distal, and one arose in the body. Intestinal metaplasia was found in three out of five; in one there was no antral mucosa in the specimen, and in another sampling was very limited. All tumours were strongly positive for CAM5.2. Rudimentary glandular formation was seen in some tumours. All were well circumscribed and in one tumour the pleomorphic inflammatory tumour occurred as a well-defined component of a mixed tumour, clearly demarcated from typical intestinal adenocarcinoma on one side and mucinous adenocarcinoma on the other.

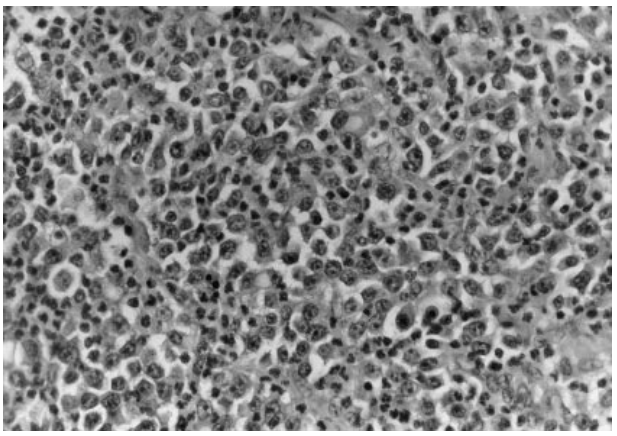

Figure 1. Large discohesive and highly pleomorphic cells intermingled with abundant neutrophil polymorphs.

We have not encountered descriptions of this histological pattern in the standard textbook accounts of gastric carcinoma, although interestingly there is a case report of a systemic polymorph leucocytosis associated with gastric cancer.[2] We believe that gastric carcinoma with extensive neutrophilic infiltration is a variation on the theme of gastric adenocarcinoma, arising in the usual background of chronic gastritis, and, on the basis of this very small sample, that it confers no particular advantage in terms of prognosis. However, since its pleomorphic and inflammatory pattern is preserved in the nodal metastases there is the potential for confusion with the entity described by McCluggage.

The finding of extensive neutrophil polymorph infiltration in some gastric cancers is no doubt related to secretion of the chemotactic cytokine interleukin-8 (IL-8) and other chemokines. Immunoreactive IL-8 has been demonstrated in gastric carcinoma cells from both intestinal and diffuse types,[3] and the presence of an inflammatory cell infiltrate within tumours has been explained by the capacity of some carcinomas, such as transitional-cell and renal-cell carcinomas, to secrete IL-8.[4]

Studies aimed at determining the prevalence of gastric carcinomas with extensive neutrophil infiltration and

its influence on prognosis after potentially curative resection are currently underway.

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Misleading PSA immunopositivity

Sir: A recent paper by Simpson and Skalova[1] describes two cases of metastatic carcinoma of the prostate presenting as a parotid tumour. This paper referred to research by van Krieken[2] describing positive staining for prostatic specific antigen in 50% of pleomorphic adenomas of the salivary gland and that they were not aware of anyone reproducing these findings. This prompted Henwood[3] to draw attention to the fact that striated duct cells in the salivary gland can stain immunohistochemically for prostatic specific antigen.

Interestingly, a recent case report[4] has demonstrated scattered positivity for prostatic specific antigen in a pleomorphic adenoma (benign mixed tumour) of the female breast. Clearly as mixed cell tumours, similar to those in the salivary gland, can be found at a variety of body sites care needs to be taken when assessing staining for prostatic specific antigen, particularly if the biopsies are small and the diagnosis morphologically is not immediately apparent. Furthermore, the finding of prostatic specific antigen expression at other body sites and in the tissue samples from women raises some interesting molecular questions!

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Why classify basal cell carcinomas?

Sir: Most current reports of basal cell carcinoma within the United Kingdom probably contain insufficient information. Accordingly, Professor Rippey must be congratulated in attempting to improve this situation.[1] As histopathologists, we should certainly be reporting those features that are more frequently associated with aggressive growth, local recurrence and metastatic spread. The features suggested by Professor Rippey are an admirable and acceptable start. I await with interest, however, to see whether the identification of micronodular growth proves to be reliable between different observers.

In broad terms, Professor Rippey has contributed significantly to the development of a minimum dataset for basal cell carcinoma. His traditional approach to this area is, however, open to comment. Clinical medicine is now increasingly being placed on a firm scientific basis by the use of robust information, such as that provided by randomized controlled trials and meta analysis. With the exception of multivariate analysis, such an approach is, however, poorly developed in histopathology. In general, there is a tendency for authors to simply quote a small number of selected papers to support their case. In essence, compared to clinical medicine, histopathologists are generally requested to accept new approaches that are centred on a less than perfect evidence-base. The question we should therefore ask is how best to improve and critically assess the evidence and accordingly which papers we should then accept or reject. Until this is agreed, no classification or minimum dataset should be too dogmatic.

Detailed information on excision margins and implications for wider excision is a vital aspect of reporting malignant melanoma. Although only briefly mentioned by Professor Rippey, both basal and squamous cell carcinoma warrant similar detailed attention.

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Duodenal 'pseudolipomatosis'

Sir: Stebbing and Wyatt's recent description of gastric pseudolipomatosis[1] prompts us to report a case of duodenal pseudolipomatosis, which also does not appear to have been recorded previously.

A 68-year-old man with diabetes mellitus underwent upper gastrointestinal endoscopy for the investigation of iron deficiency anaemia. The endoscopic appearances were considered to be normal, and two biopsies were taken from the second part of the duodenum to exclude coeliac disease. One of these was histologically normal, but the other showed a number of clear, rounded, PAS-negative vacuoles of varying size within the lamina propria (Figure 1), and an appearance identical to that of gastric pseudolipomatosis described by Stebbing and Wyatt and to colonic pseudolipomatosis as described originally by Snover *et al*.[2] The vacuoles caused mild expansion of the villous cores and separation of crypts and the superficial Brunner's glands that were present in the biopsy. The biopsy was otherwise normal, and in particular there was no epithelial abnormality, no mucosal atrophy and no increase in lymphoid cells or lamina propria PAS-negative macrophages. Immuno and lectin histochemistry for endothelial markers (CD34, von Willebrand factor and *Ulex europeus*) excluded lymphangiectasia. Material from the block was reprocessed for electron microscopy, which showed extracellular clear vacuoles bounded by collagen and ground substance that compressed lamina propria stromal and mononuclear cells. No other ultrastructural abnormality was apparent.

Colonic pseudolipomatosis is now considered to be an iatrogenic change in large bowel biopsies that results from penetration of gas into the mucosa during colonoscopy,[2–4] although it may also be seen as part of the morphological spectrum of pneumatosis coli in resection specimens.[5] It may be precipitated by minor trauma during endoscopy and is particularly likely to occur when hydrogen peroxide is used to sterilize endoscopes.[3,4] Stebbing and Wyatt's suggestion that pre-existing mucosal atrophy predisposes to pseudolipomatosis by rendering the mucosa less able to withstand increased intraluminal gas pressure is supported by our impression that it is commoner in colorectal biopsies from patients with inactive chronic colitis. However, in our case no apparent predisposing factor could be identified: hydrogen peroxide had not been used as a disinfectant, the endoscopy procedure had been uneventful, and there was no evidence of pre-existing duodenal atrophy.

Apart from its phenomenological interest, we report the case to illustrate that duodenal pseudolipomatosis should enter into the differential diagnosis of other small intestinal conditions that may have clear vacuoles in the lamina propria on an H & E section, notably lymphangiectasia and Whipple's disease, which can be excluded by the use of appropriate histochemistry.[6]

Figure 1. Duodenal biopsy showing rounded vacuoles in the lamina propria causing separation of crypts and Brunner's glands (bottom left) and mild expansion of villous cores (H & E×150).

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Pilomatrixoma-like visceral carcinomas

Sir: We wish to comment on a report of pilomatrixoma of the ovary by Alfsen and Strøm.[1] The authors cited a report of ovarian adenosquamous carcinoma with shadow cells[2] and proposed that most likely origin of such a tumour is a mature teratoma, in which a malignant transformation occurred. However, in agreement with Fang *et al.*, we believe that this case more probably represents an adenosquamous carcinoma with 'shadow cell differentiation' because it showed, besides pilomatrixoma-like areas, the endometrioid and neuroendocrine features unlike of pilomatrixoma.

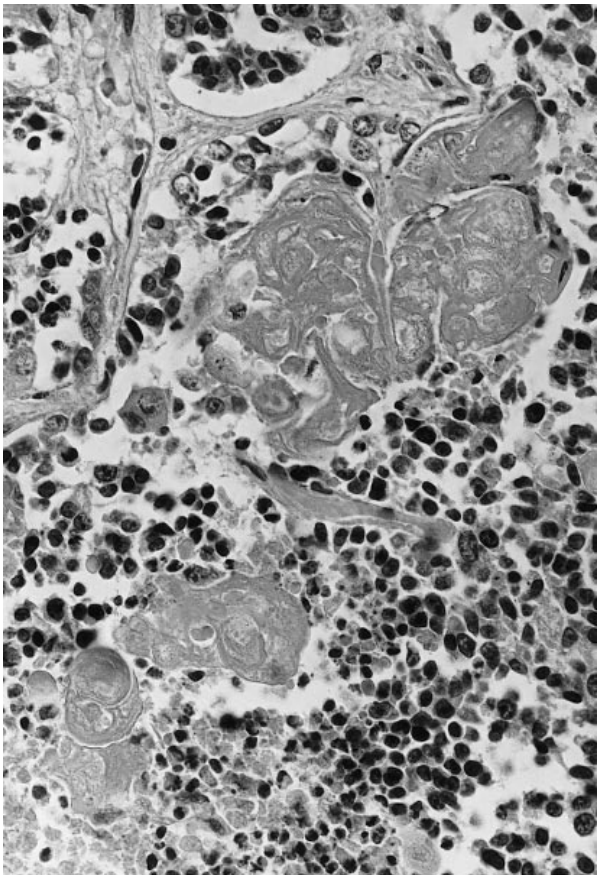

Figure 1. Shadow cells within the nests of small cell carcinoma of the gallbladder in a 67-year-old women (an autopsy case), resembling a pilomatrix carcinoma (H & E, original magnification ×160).

We would like to stress that the finding of shadow cell differentiation, which is otherwise typical of pilomatrixoma, may be seen in adenosquamous carcinomas of the uterus or in other visceral carcinomas. We found this differentiation in endometrioid carcinomas, atypical hyperplasia of endometrium, adenosquamous carcinoma of the colon,[3] transitional cell carcinoma of the bladder,[4] and recently in basaloid carcinoma of the anorectal region and in small cell neuroendocrine carcinoma of the gallbladder.[5] According to our experience, the finding of shadow cells is quite frequent in endometrioid adenosquamous carcinomas. We have found these cells in six of 100 adenocarcinomas of the uterine corpus.[5]

The pathologist should be aware that shadow cell differentiation may occur in visceral carcinomas and that it is not diagnostic of pilomatrixoma or pilomatrix carcinoma, particularly in extracutaneous locations. Also in cutaneous and subcutaneous locations there is a need to exclude a metastasis from visceral carcinoma with shadow cell differentiation before making a diagnosis of pilomatrixoma, pilomatrix carcinoma or other cutaneous tumour with shadow cells. Visceral carcinomas composed exclusively of small and shadow cells and lacking glandular differentiation may mimic a malignant pilomatrixoma (Figure 1).

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