

tions or in apparently healthy men, and thus has a role in male fertility. Several questions remain to be elucidated, such as the exact origin of those epithelial cells (i.e. rete testis, efferent ductules, epididymis, vas deferens) and the rate of disposal of spermatozoa and leucocytes by this means. Morphometric analysis with a large sample of infertile (infected and uninfected) and healthy men may be useful to assess this latter point.

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Hydroxycarbamide-induced pneumonitis

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Sir: Drug-induced lung disease can be associated with almost every pattern of described interstitial lung disease, including non-specific interstitial pneumonia, diffuse alveolar damage, organizing pneumonia or granulomatous interstitial pneumonia. Whereas some drugs can produce a relatively pure histological pattern, making the classification straightforward, other drugs can give rise to a variety of complicated histological patterns. Hydroxycarbamide (hydroxyurea)-induced lung disease has been described in only a few previous cases with poorly characterized pathology. We present a case of putative hydroxycarbamide-

induced lung disease showing a mixed pattern of cellular and fibrotic interstitial pneumonia with granulomas, in keeping with a hypersensitivity reaction.

A 62-year-old female never smoker was admitted with several months of non-productive cough and increasing breathlessness on exertion. She had taken hydroxycarbamide 500 mg daily for >12 years prior to presentation for polycythaemia rubra vera. There had been no relevant environmental or occupational exposures. Oxygen saturation was 87% on air and there were fine inspiratory lower and midzone bibasal crackles; finger clubbing was absent. Renal biochemistry, eosinophil counts and autoantibodies were negative. Her chest X-ray showed widespread bilateral interstitial infiltrates and a high-resolution computer tomography scan demonstrated interstitial change with diffuse ground glass opacification with mosaic pattern throughout both lung fields and nodularity in the upper lobes. Her spirometry was restrictive; forced expiratory volume in 1 s and forced vital capacity were 0.9 and 1.3 l, respectively (predicted 2.2 and 2.6 l, respectively). In view of the uncertain nature of the interstitial lung disease, the patient proceeded to have a lung biopsy.

Right upper and lower lobe samples obtained by video-assisted thoracoscopic surgery (VATS) were unremarkable macroscopically. Histology of these showed a widespread mixed cellular and fibrotic inflammatory cell interstitial infiltrate (Figure 1) without obvious subpleural or centriacinar accentuation, the changes classifiable as non-specific interstitial pneumonia. Focal areas of organizing intra-alveolar exudates (organizing pneumonia) and clusters of alveolar macrophages were present. Interstitial neutrophil polymorphs could also be found in a patchy distribution but without evidence of capillaritis. Eosinophils were absent. Several well-formed granulomas were identified, some situated in otherwise non-inflamed periacinar parenchyma, others seen within pulmonary vessels, pulmonary airways and interstitium in conjunction with interstitial pneumonitis (Figure 2). The pulmonary arteries revealed marked intimal thickening.

Subsequent follow-up of the patient over 6 months has revealed improvement in pulmonary function, gas exchange and radiological abnormalities since stopping the drug.

Hydroxycarbamide (hydroxyurea) is used as cytoreductive therapy in the management of myeloproliferative disorders. It exerts its effects by inhibiting the enzyme ribonucleotide reductase, which has a rate-limiting role in the regulation of DNA synthesis. The pulmonary toxicity of hydroxycarbamide is recog-

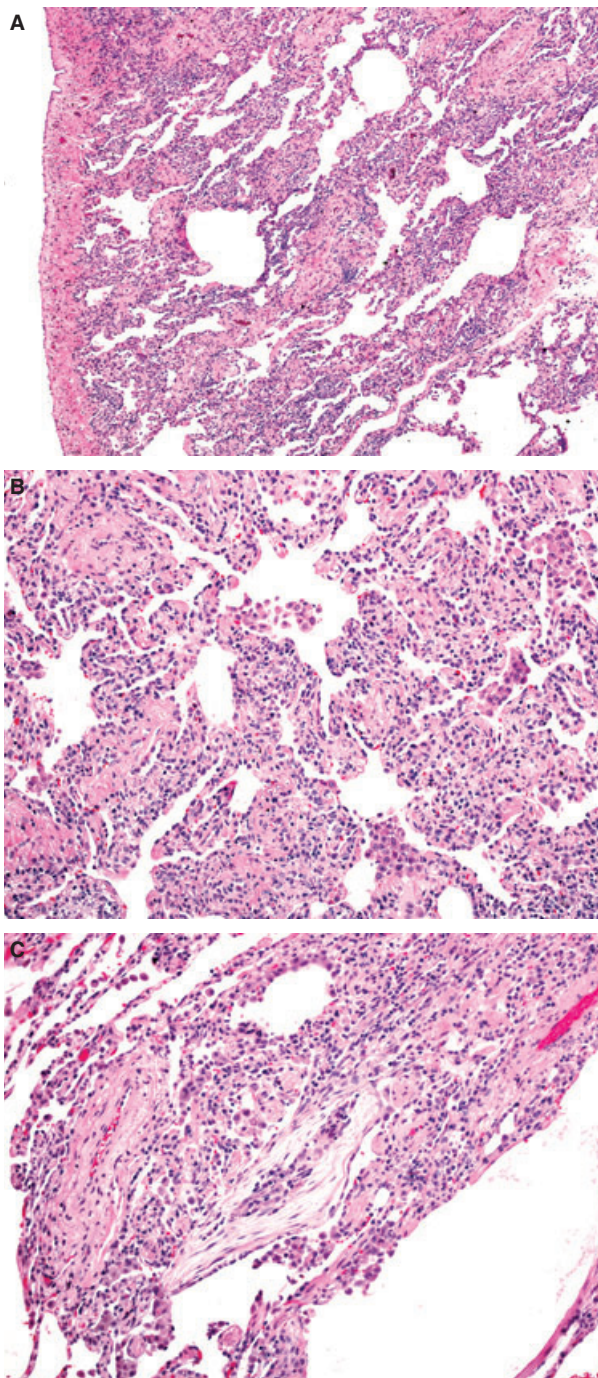


Figure 1. A, Widespread interstitial pneumonia of non-specific interstitial pneumonitis pattern. This process extends to the pleura. There is no centrilobular predominance (H&E). B, Expansion of alveolar walls by a predominantly lymphocytic infiltrate. Some neutrophils are also present (H&E). C, Focus of organizing intra-alveolar exudate (organizing pneumonia pattern) (H&E).

nized.¹⁻⁹ However, only three cases have described pathological findings, and these are rather non-specific: non-specific interstitial fibrosis and pneumocyte

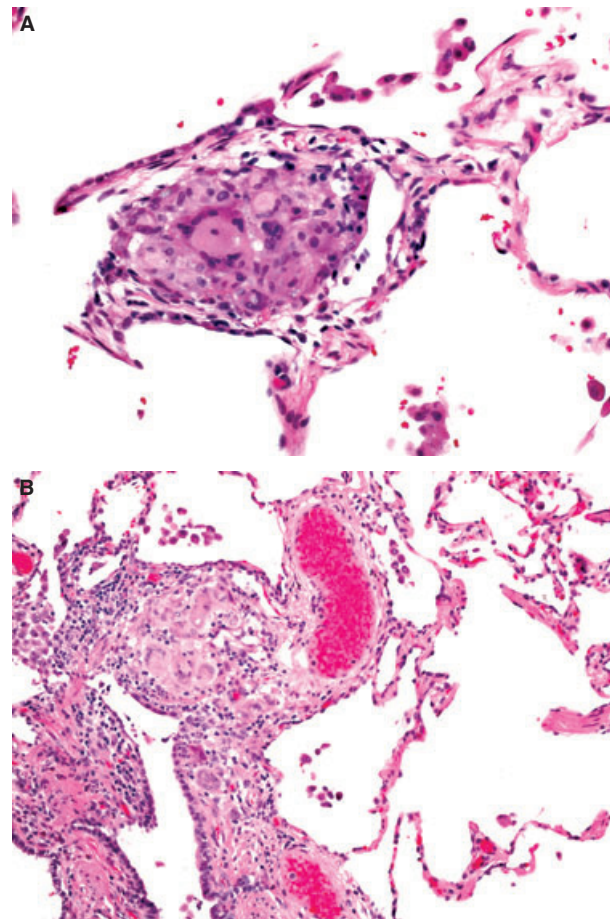


Figure 2. A, Small non-necrotizing granuloma in lung parenchyma devoid of other inflammation (H&E). B, Peribronchiolar non-necrotizing granuloma. Bronchiolitis is minimal, alveolitis is absent (H&E).

hyperplasia,¹ a desquamative interstitial pneumonitis pattern³ and marked interstitial inflammation with poorly formed granulomas.⁷ In our case, the presence of mixed cellular and fibrotic inflammation within the interstitium together with granulomas raised the possibility of hypersensitivity pneumonitis (HP), although the pattern of distribution was not typical. Some bronchiolar granulomas were identified, but others were observed in non-inflamed parenchyma and, more importantly, the interstitial pneumonia did not have a centrilobular distribution. Typical HP is related to allergen inhalation. The more diffuse distribution of changes in this case could represent a hypersensitivity reaction to the drug and/or its breakdown product(s) being distributed in the lung by the bronchopulmonary circulation. The microanatomical distribution of pathology can only be appreciated on larger lung samples. Transbronchial lung biopsy is unsuitable for such assessment and an open or VATS lung biopsy is considered the gold standard.

In everyday practice, the diagnosis of drug-induced lung disease is often made on clinical grounds, without biopsy and pathological diagnosis, in turn explaining why detailed descriptions of some drug-induced lung diseases are scarce.

This case is the first detailed pathological description of hydroxycarbamide-induced pneumonitis. The mixture of pathology present suggests a type III/IV hypersensitivity response in a 'random' distribution, consistent with a blood-borne allergen.

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HER-2/Neu overexpression is a rare event in peri-ampullary cancer: assessment using the HercepTestTM

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Sir: HER-2/neu is overexpressed in 0–82% of cases of pancreatic cancer.^{1–4} This wide variability may be due

to the type of antibodies used, their epitope binding affinities/specificities or interobserver variability.⁵ Koeppen *et al.*³ demonstrated, in a large series of archived paraffin-embedded tissue, that HER-2/neu is rarely (1/99) overexpressed in pancreatic cancers. Clinical trials using trastuzumab are based on an accurate assessment of HER-2/neu status, and the findings of Koeppen *et al.*³ cast doubt on the wide applicability of such treatment for pancreatic cancer. However, there are no published studies of HER-2/neu assessment in pancreatic cancer strictly following the universally accepted HercepTest protocol (Dako, Glostrup, Denmark), which is the current standard, approved by the Food and Drug Administration for assessing HER-2/neu status in patients with breast cancer.⁶

In order to verify the results of Koeppen *et al.*,³ we carried out immunohistochemistry in a range of peri-ampullary cancers using the HercepTestTM. Tissue microarrays (TMAs) were constructed using triplicate cores from random areas within regions of interest in archived formalin-fixed tissue from 126 consecutive patients who had undergone pancreatic resections. Cancer was present in 104 patients (pancreatic ductal adenocarcinoma = 38, ampullary adenocarcinoma = 22, cholangiocarcinoma = 29, duodenal adenocarcinoma = 5) and 22 had chronic pancreatitis. Specimens of reactive pancreatitis were obtained from areas adjacent to the cancer in 78 patients. Normal pancreatic tissue was obtained from the resection specimens, adjacent to areas of cancer or chronic pancreatitis in 30 patients. TMAs were also constructed from 61 metastatic lymph nodes from 61 patients. Immunohistochemistry of thin sections for HER-2/neu was carried out in accordance with the manufacturer's instructions⁷ (HercepTestTM, Dako). HER-2/neu immunoreactivity was quantified as follows: 0, no membranous reactivity; 1+, barely perceptible reactivity not totally encircling the cell membrane; 2+, light to moderate reactivity totally encircling the cell membrane; and 3+, moderate to strong reactivity totally encircling the cell membrane. Tissues with 2+ or 3+ reactivity shown in at least 10% of cells were classified as overexpressing HER-2/neu. Breast carcinoma was used as a positive control (Figure 1).

Only one of 104 cancers was immunopositive (3+) for HER-2/neu overexpression (Figure 2). This was a pancreatic ductal adenocarcinoma and showed strong membranous reactivity. Of the remaining 103 cases, five cancers (two ampullary adenocarcinomas and three ductal adenocarcinomas) showed 1+ reactivity. The remaining malignant and benign tissue did not express HER-2/neu.