Case report

Wegener's granulomatosis with granulomatous liver involvement

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ABSTRACT

We report on a patient with biopsy proven systemic Wegener's granulomatosis (WG) with a granulomatous necrotising manifestation of WG in the liver, lung, parotid gland and skin with subsequent death of liver failure. Liver involvement in WG is an exceedingly rare, though potentially fatal organ manifestation of WG.

Case report

A 72-year-old female was admitted to another hospital with facial paresis resulting from a necrotising granulomatous parotitis and granulomatous vasculitis of the parotid gland (Fig. A). At the same time, multiple small bilateral pulmonary opacities as well as a focus of the left lower lung field were radiologically detected. Subsequent biopsy of the left lung focus yielded a granulomatous inflammation with necrotising granulomas of lung tissue without vasculitis, retrospectively well consistent with WG (Fig. B). Mycobacterial or fungal infection as well as neoplastic disease was excluded; a diagnosis of WG was made and the patient was started on 50 mg steroids. Initial ANCA testing was not documented. After two years, steroids were tapered as the patient was without symptoms of active disease. One year later, a chest x-ray taken during a stay in the surgical department showed bilateral opacities that were interpreted as pneumonic though they only partially subsided after antibiotic therapy. Recurrent WG was not considered at this time; no immunosuppressive therapy was reinstalled. Nine months later, the patient presented to our unit with weight loss, multiple hepatic lesions measuring up to 4 cm, bilateral pulmonary infiltrates as well as a subcutaneous abdominal nodule. Liver enzymes were ALAT 62 U/l, γ-GT 151 U/l, AP 299 U/l, CRP was 70 mg/l. No renal involvement was present. Biopsies of liver (Fig C-D), lung and skin were obtained. The hepatic tissue was infiltrated by confluent ill-defined epitheloid cell granulomas with extensive necrosis. The histological findings in the other affected organs were also consistent with WG showing non-necrotising epitheloid cell granulomas in the lung and subcutaneous granulomatous inflammation with vasculitis. Tuberculosis and fungal infection were again excluded. P-ANCA and c-ANCA were negative. A diagnosis of ANCA-negative WG was made. Prednisolone was started at 50 mg qd, since other immunosuppressive therapy was declined. The patient then saw another physician who started cyclophosphamide (CYC) therapy 8 months later. After 5 boli of CYC lung and skin were in remission; however, 2 months later the patient developed jaundice and elevated liver enzymes (total bilirubin of 25 mg/dl, γ-GT of 1772 U/l and impaired coagulation parameters). The liver biopsy again showed a similar picture as before therapy with granulomatous hepatitis, tissue destruction and necrosis. Autoimmune hepatitis and viral hepatitis were excluded. Under a therapy of 100 mg prednisolone qd, liver enzymes decreased. Liver transplantation was declined and the patient died of liver failure 3 years later, *i.e.* 8 years after primary manifestation of WG.

WG can principally affect any organ in a vasculitic or granulomatous disease pattern. The respiratory tract is preferentially affected with granulomatous disease, possibly as a result of a disturbed mucosal barrier interaction with an exogeneous antigen hitherto not known (1). Primary manifestation in salivary glands can occur (2). Involvement of the liver in WG has been

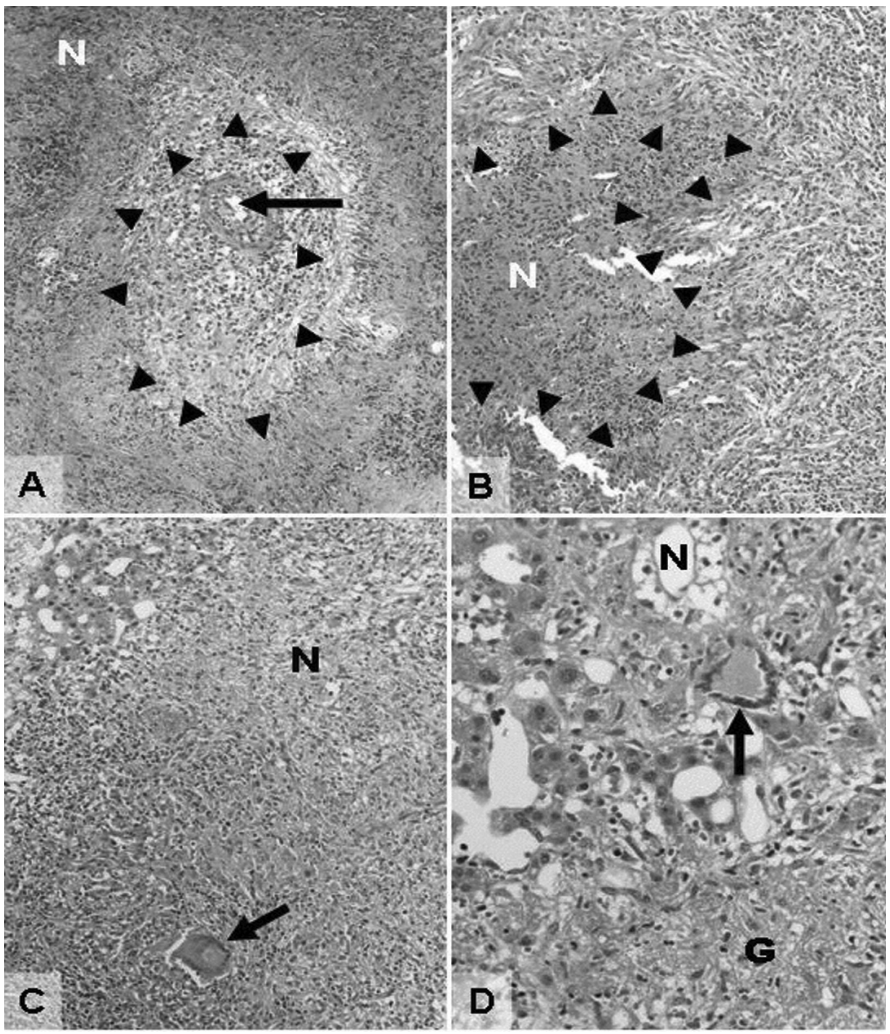

Fig. 1A. Granulomatous necrotising vasculitis in parotid gland. Vasculitis with highly narrowed small arterial lumen (arrow) and perivascular concentric epitheloid cell granuloma (arrow heads). Necrotic salivary gland tissue (N). No intact glandular tissue preserved. (H&E, original magnification x 100).
B. Geographical necrosis of lung (N) with surrounding ill-defined granulomatous tissue and dense fibrosis. Geograpical shaped outlines of necrosis highlighted by arrow heads. (H&E, original magnification x 100).
C. Liver biopsy showing extensive necrosis (N) and adjacent ill-defined granulomatous infiltrates with a giant cell of Langhans' type (arrow). (H&E, original magnification x 100).
D. Liver biopsy (detail) with epitheloid cell granuloma (G), giant cell of Langhans' type (arrow) and confluent necrosis (N). (H&E, original magnification x 200).

described in 2 of 3 autopsy cases by Alfred Wegener in his original publication (3) with intrahepatic vasculitis, albeit no granulomatous liver disease. A systematic review of the literature in the Pubmed database (1966-2009) revealed only one report on granulomatous liver involvement in WG in a single autopsy case (4) and one case report of autoptically proven vasculitic hepatic involvement (5). No information was available in Pubmed on therapeutic strategies for liver involvement in WG. Among the 180 WG patients of the WGET study (6), no hepatic involvement was described. The Se.Pri.Va. study group (7) found elevated liver enzymes at the time of diagnosis in 8-11% of 36 WG patients as a prognostically adverse sign, however, the histological type of tissue damage is not specified. Conversely, in their large retrospective study of 63 liver biopsies with granulomatous disease (out of a total of 1662) Gaya *et al*. found no cases of WG (8). A further Pubmed analysis of the literature (1966-2009) retrieved one report of non-caseating granulomatous hepatitis in a WG patient as a rare adverse effect of CYC which responded to CYC withdrawal (9). In our case, an adverse drug effect of cyclophosphamide could be excluded, since the lesions had already been present before CYC therapy. The type of ill-defined necrotising granuloma found in the liver is typical of WG granulomas, corresponding to the granulomatous disease in the other affected organs lung, parotid gland and skin. Granulomatous liver involvement resulted in fatal liver failure 8 years after disease onset. This is in keeping with a systematic review on mortality in systemic vasculitis by Phillip and Luqmani (10) who found persistent active disease as one of the major causes of late death in WG. Necrotising granulomatous hepatitis therefore is an extremely rare but potentially fatal organ manifestation of WG.

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