The Significance of Extracapillary Proliferation

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Summary
Renal biopsy and clinical data from 60 patients with crescent formation were correlated. Nephropathy was related to infection (15 cases), malignancy (four) and trichlorethylene exposure (two). Four cases had extrarenal signs. Isolated proteinuria was found 0.5–20 yr before biopsy in 16. Only 17 patients had rapidly progressive glomerulonephritis on clinical criteria. Nineteen patients (35%) are alive with functioning kidneys. Outcome was significantly related to percentage crescentic involvement (p < 0.02) and oliguria (p < 0.05) and renal function (p < 0.01) at presentation. Preceding infection was a favourable sign.

Extracapillary glomerulonephritis is not a single entity.

Introduction
The relationship between the presumed morphological entity ‘extracapillary glomerulonephritis’ of Volhard and Fahr (1914) and the clinical syndrome of rapidly progressive glomerulonephritis remains a subject of debate.

This report attempts to analyse the clinico-pathological significance of extensive crescent formation in adults. Crescent formation may occur as a primary glomerular disease or secondary to other glomerular lesions (Habib, 1973; Heptinstall, 1973; Pollack and Mendoza, 1971). Patients with definite periarteritis nodosa, systemic lupus erythematosus and Henoch–Schönlein purpura were excluded from the study.

HISTOLOGIC FEATURES
Criteria for inclusion were essentially morphologic. All biopsies included a minimum of eight glomeruli on light microscopy with crescent formation, extracapillary proliferation, in at least 50% of the glomeruli of 60 patients. In 44 patients material was available for immunofluorescence (minimum five glomeruli).
More than 80% glomerular involvement by crescents has been regarded as the morphological equivalent of rapidly progressive glomerulonephritis, indicating a particularly poor prognosis (Royer et al, 1973). Thus, 31 patients with more than 80% glomerular involvement (group I) were analysed separately from the 29 others with 50–80% involvement (group II).

Histological changes were graded semi-quantitatively from 0 to +++ and analysed using a Chi-square test.

The percentage glomerular crescentic involvement was significantly correlated with crescent size (p < 0.01), interstitial infiltration (p < 0.01), interstitial fibrosis (p < 0.02) and tubular lesions (p < 0.05). In practical terms, the close correlation between crescent size and percentage of glomeruli involved by crescents meant it was not necessary to examine prognosis in terms of percentage glomerular area involved, as suggested by Lawrence, 1973. Similarly, interstitial infiltration, fibrosis and tubular lesions all correlated with the number of glomeruli involved and thus it was not necessary to assess outcome in terms of interstitial disease as Striker et al (1973) have done.

Endocapillary proliferation in so-called extracapillary glomerulonephritis is absent in reports from American authors (Bacani et al, 1968) but invariable in the Australian experience (Mathew and Kincaid-Smith, 1973). We found hypercellularity very difficult to assess in contracted tufts but about one-third of our cases did not show any proliferation and another third had moderate to extensive proliferation.

Fibrinoid necrosis defined as a partial loss of glomerular structure with replacement by bright pink material on trichrome stain was present in only half our biopsies. This is evidently less than in Australia where this entity is called 'fibrin and crescent glomerulonephritis' (Mathew and Kincaid-Smith, 1973) but possibly in France patients are biopsied at a later stage.

<table>
<thead>
<tr>
<th>TABLE I. Immunofluorescent Patterns in 44 Patients with Extracapillary Proliferation</th>
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<tr>
<td>Fibrinogen without immunoglobulin (non-immunologic injury)</td>
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<tr>
<td>Diffuse granular immunoglobulin and complement (immune-complex)</td>
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<td>Linear immunoglobulin (anti-GBM antibody)</td>
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<td>Focal immunoglobulin or complement (localized damage)</td>
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<tr>
<td>Negative</td>
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<tr>
<td>Total</td>
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Polymorphonuclear infiltration was evident in about one-quarter of cases and was significantly related to the degree of tuft proliferation.

On immunofluorescence, biopsies were classified as shown in Table I.

Immunofluorescent findings were thus variable and difficult to classify. Focal fibrinogen, usually in crescents or presumably necrotic foci in the tufts, was absent in 20% of biopsies.

Linear immunoglobulin was uncommon, being found in only six cases, and
was associated with linear β1C in only one case. Anti-glomerular basement membrane antibody was found in one of four cases tested.

The great variety of patterns seen suggest multifactorial aetiology and indicate that extracapillary proliferation is not a single morphological entity.

**CLINICAL FEATURES**

Proteinuria was known to have been present for from at least six months to 20 years in 16 patients, four of whom had associated microscopic haematuria.

Preceding infection was present in 15 patients. In seven cases, it was a sore-throat, but definitely streptococcal in only one patient. One patient had sub-acute bacterial endocarditis and the other seven had suppurative lesions, in lungs, abdomen or nasopharynx.

In four patients the onset of nephropathy was closely associated with the diagnosis of malignancy. Lesions were found in lung and breast. Secondary deposits and basal cell carcinoma were also found.

Four patients had features suggestive of multisystem disease but the diagnosis remained unproven.

Two patients give a history of occupational exposure to trichlorethylene.

The male: female ratio was 1.8:1, the mean age was 38 yr and age range 15-75 yr.

At presentation, microscopic haematuria with more than 5000 erythrocytes/ml was present in all patients and in seven it was macroscopic. Proteinuria of more than 0.5 g/day, was present in all except one patient and 18 were frankly nephrotic. Oliguria with less than 600 ml urine/day was present in 21 patients at presentation and the blood pressure was over 150/90 mm Hg in 26. A reduced GFR, with clearance below 60 ml/min, was found in 47 patients. Two patients presented with features of acute glomerulonephritis and 11 were febrile on admission.

Five of 40 patients tested had an elevated antistreptolysin titre (>300 u), 2/29 had depressed serum complement levels, and 13/28 had a cryoglobulin. The outcome in these 60 patients is shown in Table II.

<table>
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<tr>
<th>TABLE II. Outcome in 60 Patients with Extracapillary Proliferation</th>
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<tr>
<td>Dead</td>
</tr>
<tr>
<td>Dialysis</td>
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<tr>
<td>Functioning graft</td>
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<tr>
<td>Renal insufficiency</td>
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<tr>
<td>Normal function</td>
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<tr>
<td>Lost to follow-up</td>
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<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

The cumulative five-year survival (Cutler and Ederer, 1958) was 23 ± 8%. The outcome was correlated with percentage glomerular crescentic involvement
(p < 0.02), oliguria at presentation (p < 0.05) and impaired renal function at presentation (p < 0.01). Preceding infection was a favourable prognostic sign (p ≈ 0.05).

Thirteen patients in group I and four in group II died or required maintenance haemodialysis within six months and so could be truly regarded as rapidly progressive glomerulonephritis. However, group I was not always associated with a rapidly progressive course. Seven patients have renal function compatible with normal activity up to six years after presentation and nine others have lost all renal function only after between one and five years.

Extracapillary proliferation may occur in primary or secondary glomerular disease. Clinical and morphological features indicate that extracapillary glomerulonephritis is not a single entity. More than 80% glomerular involvement by crescents does not necessarily imply rapidly progressive glomerulonephritis. The prognosis is grave but the lesion is sometimes reversible.

Acknowledgments

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