29 - Light chain deposition disease

In light chain deposition disease:
- Renal impairment or nephrotic syndrome is often a presenting feature.
- Approximately two-thirds of patients have an underlying lymphoplasmacytic proliferative disorder, such as multiple myeloma.
- An abnormal $\kappa/\lambda$ sFLC ratio is present in around 90% of patients at diagnosis.
- sFLCs are useful for monitoring disease, and are recommended in International Myeloma Working Group guidelines.

29.1. Introduction

The rare monoclonal immunoglobulin deposition diseases (MIDD) comprise light chain deposition disease (LCDD), light- and heavy-chain deposition disease (LHCDD) and heavy-chain deposition disease (HCDD) \(^2\). In LCDD, which comprises 80% of the cases of MIDD \(^1\), monoclonal serum free light chains (sFLCs) are precipitated on basement membranes in the kidneys and less frequently, the heart, liver and other organs. Deposits can be visualised by staining of biopsy samples (Figure 29.1). As with AL amyloidosis, the disease is progressive and leads to failure of the affected organs and has a poor prognosis \(^2\). However, LCDD differs from AL amyloidosis in a number of ways: 1) it is more frequent in younger women (aged 30 - 50 years); 2) renal failure is a common presenting feature; 3) the predominant light chain type is $\kappa$ (typically $V_\kappa 1$ and $V_\kappa 4$), rather than $\lambda$; and 4) light chain deposits do not contain serum amyloid P component (SAP, a protein that typically localises in areas of amyloid) and are congo red negative.

Approximately two-thirds of patients with LCDD have an underlying lymphoplasmacytic proliferative disorder: A study by Pozzi et al. \(^3\) reported that out of 63 patients with LCDD, MM was diagnosed in 65% of cases, whilst chronic lymphocytic leukaemia was present in a further 3% of cases. The remaining 32% of patients did not have any detectable haematological disease. Whilst monoclonal proteins are detectable by serum or urine immunofixation electrophoresis in the majority of patients (76 or 90% of cases, respectively) \(^5\), the concentrations may be low \(^6\) and difficult to monitor.

29.2. sFLC assays support a diagnosis of LCDD

A diagnosis of LCDD should be suspected in all cases of renal insufficiency of unknown origin. Whilst a definitive diagnosis of LCDD is based on renal biopsy with thorough histological examination and electron microscopy \(^5\), sFLC analysis should be included in the initial laboratory testing algorithm as the majority of patients have monoclonal sFLCs. This was demonstrated by Katzmann et al. \(^7\) for 18 LCDD patients who were included as part of a larger study aimed at evaluating different serum- and urine-based diagnostic algorithms. The analysis showed that sFLC testing alone, or a panel of serum protein
electrophoresis (SPE) and sFLCs, were both as sensitive (14/18; 77.8%) for LCDD detection as a panel of SPE, serum immunofixation electrophoresis (sIFE) and urine IFE (uIFE). Guidelines published by the International Myeloma Working Group (IMWG) [9] recommend the use of sFLC analysis in combination with serum electrophoresis to screen for monoclonal gammopathies, with the exception of AL amyloidosis which additionally requires a 24-hour uIFE. European Myeloma Network recommendations also state that FLC measurements along with sIFE and uIFE are required for the diagnostic evaluation of patients with suspected MIDD [9]. Screening algorithms are discussed further in Chapter 23 and guidelines are detailed in Chapter 25.

The above study by Katzmann et al. [7] supports two previous studies by the same authors in which the diagnostic sensitivity of sFLC analysis in LCDD was evaluated. In one study [10], 89% (17/19) of patients with LCDD had an abnormal κ/λ sFLC ratio, including 6/7 patients who were negative by sIFE (Table 29.1). One sample was negative by sFLC analysis but positive by sIFE. In a subsequent publication, seven further patients were studied and all had abnormal κ/λ sFLC ratios [7].

<table>
<thead>
<tr>
<th>Classification</th>
<th>Elevated FLC</th>
<th>Abnormal FLC κ/λ ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>sIFE κ +ve</td>
<td>8/9</td>
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</tr>
<tr>
<td>sIFE λ +ve</td>
<td>3/3</td>
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</tr>
<tr>
<td>sIFE -ve; uIFE κ +ve</td>
<td>4/4</td>
<td>4/4</td>
</tr>
<tr>
<td>sIFE and uIFE -ve. BMPCs κ +ve</td>
<td>1/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Total abnormal for sFLCs</td>
<td>16</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 29.1. Detection rates by sFLCs in 19 LCDD patients. BMPC: bone marrow plasma cells.

The diagnostic sensitivity of sFLC analysis for LCDD demonstrated above by Katzmann et al. has similarly been shown by other researchers. In the largest single-centre series of renal MIDD published to date, Nasr et al. [1] reported that κ/λ sFLC ratios were abnormal in all patients tested (43/43 LCDD, 4/4HCDD and 4/4 LHCDD) and markedly abnormal (<0.125 or >8) in 78% of these. Cohen et al. [12] also reported abnormal sFLC ratios in 100% of patients (n=32). In a further study of 17 patients with biopsy-proven LCDD, Wechalekar et al. [13] found that 33% more patients with LCDD were identified by an abnormal κ/λ sFLC ratio than by standard electrophoretic methods, and concluded that sFLC analysis was a useful addition to electrophoretic tests when screening for LCDD. An early diagnosis can be clinically valuable as rapid treatment is fundamental for improving patient outcomes [14]. Clinical case history 1 illustrates the clinical sensitivity of the FLC tests compared with conventional serum and urine electrophoretic assays in a patient with LCDD and renal impairment.

Clinical case history 1

Light chain deposition disease undetectable by conventional electrophoretic assays [15].

A 66-year-old man suffering from asthenia and anaemia was investigated for serum protein abnormalities. SPE, sIFE and uIFE tests showed no evidence of monoclonal immunoglobulins (Figure 29). Serum immunoglobulin concentrations were normal/low: IgG 8.5 g/L; IgA 0.4 g/L and IgM 0.2 g/L. However, sFLC concentrations were highly abnormal: κ 294 mg/L; λ 71.6 mg/L and κ/λ ratio 4.1. These results indicated a monoclonal gammopathy and renal impairment. In this patient, sFLC analysis allowed the detection of monoclonal FLCs and supported the clinical diagnosis of LCDD obtained by renal biopsy.
29.3. Monitoring LCDD using sFLC assays

It is logical to monitor LCDD patients using sFLC assays. Although there is no published data formally validating the use of the sFLC assays for assessing haematological response in patients with LCDD, the personal experience of many authors confirms their utility and international and European guidelines recommend sFLC analysis for monitoring LCDD (Section 25.3.1). Clinical case history 2 illustrates the benefit of sFLC analyses in a patient who was difficult to monitor by other methods.

Wechalekar et al. monitored 10 LCDD patients receiving a range of systemic chemotherapy, (and autologous stem cell transplant [ASCT] in 2/10 cases). Eight patients had sFLC responses, with a median decrease of 63% (range 31 - 95%), compared with pre-treatment values. One patient, who had a normal sFLC ratio pre-treatment, had no change in sFLC levels but had a very good partial response of the monoclonal intact immunoglobulin post-treatment. Only two patients had complete normalisation of sFLC levels. The authors concluded that sFLC analysis was useful for monitoring responses to treatment.

Hassoun et al. reported on five patients with LCDD, one with LHCDD and one with light chain proximal tubulopathy (a disease characterized by κ-restricted crystal deposits in the proximal tubule cytoplasm). All had abnormal sFLCs at diagnosis, whereas only one patient had a monoclonal band visible by SPE and two patients had IgGκ monoclonal proteins identified by sIFE. Patients were given high-dose melphalan and ASCT with good responses that could be monitored with sFLC assays (Figure 29.3). Similarly, Jimenez-Zepeda et al. found that measurement of sFLCs was useful in the follow-up of six patients with LCDD treated with bortezomib and ASCT. All six patients had elevated sFLCs at diagnosis whereas only two patients had serum monoclonal proteins >10 g/L. A decrease in the levels of involved sFLCs was associated with a significant reduction of proteinuria. Similarly, Minarik et al. reported rapid and deep reductions in sFLC levels within two cycles of treatment with bortezomib-based induction regimens in three patients with LCDD.

Clinical case history 2

A patient with LCDD affecting the kidney, monitored with sFLC assays.

A 59-year-old Caucasian male presented to nephrologists with flu-like symptoms, hypertension and swelling of the face, hands and legs. Urinalysis revealed he had nephrotic range proteinuria (13.9 g/24 hours) and serum creatinine was elevated at 200 μmol/L. A renal biopsy showed nodular glomerulosclerosis with evidence of LCDD on electron microscopy (granular electron-dense material in the tubular basement membranes). Congo red staining was negative. Serum electrophoresis, immunoglobulin levels and urinary Bence Jones protein assays were all normal.

The patient was referred to the haematology department to rule out an underlying clonal B-cell disorder. A bone marrow aspirate and trephine revealed normal cellular marrow with no morphological or immunophenotypic evidence of MM. Congo red staining was, again, negative and a SAP scan also showed no evidence of amyloid deposition. Serum was tested for sFLCs with the following results: κ sFLC 526.0 mg/L (normal range 3.3 - 19.4 mg/L), λ sFLC 64.6 mg/L (normal range 5.7 - 26.3 mg/L) and κ/λ ratio 8.14 (normal range 0.26 - 1.65) (Figure 29.4). The patient subsequently developed atrial fibrillation. A 24-hour tape showed irregularities in the atrial chamber and intermittent disruption of AV node conduction. A dual chamber pacemaker was fitted and cardiac biopsy performed, which showed no evidence of amyloid or light chain deposition.
His hypertension was treated with an angiotensin-converting enzyme inhibitor. However, within 12 months his renal function had deteriorated further (serum creatinine reached 300 μmol/L) and he continued to have heavy proteinuria. In order to prevent further progression of his renal disease, the patient was treated with 3 cycles of VAMP chemotherapy (vincristine 0.4 mg/day for 4 days, doxorubicin 9 mg/m²/day for 4 days and methylprednisolone 1 g/m² for 5 days per cycle). Renal function subsequently improved (serum creatinine fell to ~200 μmol/L) and this was accompanied by decreasing sFLC levels and κ/λ ratio. Nine months after the chemotherapy, urinary protein excretion had fallen to 4.4 g/24 hours.

For the following year, renal function remained stable but subsequently, the κ/λ sFLC ratio and serum creatinine concentration began to increase again. The patient was treated with a further 3 cycles of VAMP and again, similar improvements in renal function and sFLC levels were seen. The authors concluded that this case was the first to demonstrate a direct relationship between the measurement of sFLCs and renal function in LCDD.
Figure 29.2. LCDD showing normal SPE (scanning densitometry) and IFE, but highly abnormal sFLCs (κ 294 mg/L: λ 71.6 mg/L and κ/λ ratio: 4.1).

Figure 29.3. sFLC responses in 5 patients with κ light chain deposition disease.

Patients received various induction therapies for MM before undergoing consolidation with high-dose melphalan and ASCT. All patients achieved a haematological complete response and normalised κ/λ sFLC ratio following ASCT. The reference interval for the κ/λ sFLC ratio (0.26 - 1.65) is indicated by the broken tramlines. Graph produced from published data[16]

Figure 29.4. Monitoring a patient with LCDD using sFLC assays.
29.3. Monitoring LCDD using sFLC assays

References


