28.5 AL amyloidosis patients with distinct clinical features

28.5.1 Cardiac amyloidosis

The deposition of amyloid fibrils in the heart leads to heart dysfunction, as the cardiomyocytes become distorted and separated and the whole tissue stiffens. At diagnosis, around half of all AL amyloidosis patients have symptomatic cardiac involvement. The most common symptom is heart failure with a preserved ejection fraction, but arrhythmias, syncope, ischemic heart disease, cardiomyopathy and thrombosis are also seen. Cardiac involvement in AL amyloidosis leads to a poorer outcome, and is correlated with the extent of cardiac deposition and severity of cardiac involvement. Cardiac involvement is the leading cause of death in AL amyloidosis patients and delayed diagnosis is correlated with shorter overall survival. Therefore rapid, correct diagnosis is vital.

To make a diagnosis of cardiac AL amyloidosis can present a challenge, firstly due to the range of symptoms, which are not specific to the condition, and secondly because cardiac amyloidosis can be caused by a number of different amyloidogenic proteins. The three most common amyloidogenic precursor proteins are immunoglobulin light chains (AL), wild type transthyretin (wt ATTR) and mutant transthyretin (ATTR). It is important to identify which protein has formed the deposits, as the treatment for each form of amyloidosis is different, and what is effective for one may not be effective for another. Identification of the amyloidogenic protein is of increased importance in aging populations, where cardiac deposition caused by wt ATTR may occur in monoclonal gammopathy patients.

The diagnostic criteria for AL amyloidosis with cardiac involvement is the same as for AL amyloidosis in general. Several groups have developed screening algorithms to identify AL amyloidosis in patients who present with cardiac symptoms. The protocol developed by Gertz et al. aimed to identify AL, wt ATTR and ATTR amyloidosis in cardiac patients with the use of minimally invasive tests. The authors proposed an initial screen of sIFE, uIFE and sFLC analysis and if a monoclonal protein is detected, a fat aspirate and a bone marrow biopsy are performed to confirm diagnosis. In his 2018 update to the algorithm, Gertz proposed the addition of a pyrophosphate uptake scan to the algorithm to help detect ATTR cardiac deposits.

Once cardiac AL amyloidosis is diagnosed, measurement of cardiac biomarkers and sFLCs are useful for determination of the prognosis, and can also be used to monitor...
28.5.2 Patients with low amyloidogenic FLCs

Up to 20% of AL amyloidosis patients have a low sFLC burden at diagnosis (dFLC <50 mg/L), and have historically been excluded from clinical trials because no haematological response criteria besides a complete response (CR) can be applied to them [13]. Two initial European studies [13][14] published in parallel characterise the distinct clinical features and outcomes of these so-called ‘low dFLC’ patients, and recent American [15] and Greek [16] studies further build on these findings. Milani et al. [14] compared 203 newly diagnosed low dFLC patients with 866 patients with measurable sFLCs, and found that low dFLC patients had a smaller plasma cell clone than those with measurable disease (median bone marrow plasma cell infiltrate 8% vs. 12%, p<0.001). This finding was confirmed by others [13][15][16][17], who also reported no significant difference in the frequency of cytogenetic abnormalities between the two groups [13][15].

Patients with low dFLC have a more favourable outcome compared to those with evaluable FLCs, regardless of treatment type [13][14][15][16][17]. For example, Milani et al. [14] reported a median overall survival of 118 months for patients with low dFLC, compared to 21 months for measurable patients (p<0.001). Although renal involvement was slightly higher (77% vs. 63%, p<0.001) and more severe in the low dFLC group, heart involvement was less common (43% vs. 83%, p<0.001) and less severe. Similar findings were reported by Sidana et al. [15], who also demonstrated that in multivariate analysis (that included dFLC, 24-hour urine protein, renal function, and cardiac biomarkers), dFLC (<50 mg/L) was an independent predictor of survival. Other groups have independently reported similar results [13][14][16][17].

Dittrich et al. [13] proposed a new low-dFLC partial response (PR), defined as a reduction of dFLC to below 10 mg/L (provided that dFLC was 20-50 mg/L at baseline). After 6 months of therapy, low dFLC patients who achieved a PR had a superior outcome compared to those who did not (median overall survival not reached vs. 92 months, p=0.004). The low-dFLC response criteria were subsequently validated by a number of other groups [14][15][16][17][18]. Milani et al. [14] also reported a prognostic benefit for low-dFLC patients who achieved an amyloid CR. However this was not confirmed by Dittrich et al. [13], who commented that the discrepancy may be due to differences in the sensitivity of immunofixation electrophoresis methods used by the two centres, and further supports the application of FLC assays in response assessment. Rezk et al. [19] have proposed alternative FLC response criteria, based on the percentage reduction in dFLC, regardless of the initial concentration and Sidana et al. [15] demonstrate that normalisation of involved FLC levels is also predictive of overall survival. Further validation of these new sFLC response categories is now required.

At disease relapse, dFLC levels are generally lower than at presentation. Palladini et al. [20] characterised 92 AL amyloidosis patients at the time of second-line therapy initiation. The median dFLC was 55 mg/L, and corresponded to 41% of the baseline value. Importantly, 48% (44/92) subjects were classed as non-measurable, but when the new threshold for assessing low-dFLC response (20 mg/L) was considered, 81% had measurable disease.

In conclusion, the subgroup of AL amyloidosis patients with low dFLC at baseline represents a distinct clinical entity with an excellent prognosis, and at disease relapse many additional patients
are classified as non-measurable. It is hoped that new low dFLC response criteria will improve the clinical management of these patients and allow the majority of them to be included in future clinical trials.

28.5.3 IgM AL amyloidosis

In around 5-7% of patients, AL amyloidosis is associated with IgM paraprotein and in over half of cases the condition is secondary to non-Hodgkin lymphoma. Although IgM AL amyloidosis shares a number of characteristics with non-IgM AL amyloidosis, it represents a distinct clinical entity. IgM AL amyloidosis is characterised by a higher incidence of lymph node and neuropathic involvement, and less severe cardiac dysfunction when compared to non-IgM AL amyloidosis. Generally, IgM AL amyloidosis patients have lower levels of iFLCs than non-IgM patients (median 63 mg/L vs. 182 mg/L), which are more commonly of the κ type (42% vs. 23%).

References

7. Muchtar E, Gertz MA, Kumar SK, Lacy MQ, Dingli D, Buadi FK, et al. Improved outcomes for


