Immunoglobulin light chain (AL) amyloidosis develops in 2% of individuals with monoclonal plasma cell dyscrasias. In this issue of ONCOLOGY, Drs. Gertz and Dispenzieri discuss AL amyloidosis, highlighting progress in the field along with outstanding challenges.

The authors present two cases that illustrate the frequent problem of late diagnosis that can arise when patients present with nonspecific clinical features. It is also possible that a lingering perception that amyloidosis is untreatable may discourage further diagnostic work-up, which generally requires biopsy confirmation, especially in the older patients among whom AL amyloidosis is most common. However, the authors emphasize that certain combinations of clinical features should trigger investigation for amyloidosis, including co-existent peripheral and autonomic neuropathy, cardiac failure in association with proteinuria or marked gastrointestinal symptoms, and left ventricular “hypertrophy” in the absence of a clear cause. The index of suspicion should be heightened in patients with monoclonal gammopathy of undetermined significance (MGUS), in whom the suspicion of transformation into AL amyloidosis may be signalled by asymptomatic proteinuria on routine dip stick testing, or by elevation of the serum cardiac biomarker N-terminal fragment of brain natriuretic peptide (NT-proBNP).[1] Regrettably, the majority of patients with AL amyloidosis present out of the blue, and there is often major amyloid involvement of at least one vital organ system at diagnosis. A recent advance that would have been informative in both patients described by Gertz and Dispenzieri is cardiac MRI,[2] which can reliably differentiate between myocardial hypertrophy and expansion of the interstitial space by amyloid deposition. Increased access to cardiac MRI has lately led to a remarkable increase in diagnosis and referral to the UK National Amyloidosis Centre of patients with senile transthyretin cardiac amyloidosis, who almost always present with heart failure associated with preserved systolic function. In addition to cardiac MRI, we have also lately validated 99m-labeled technetium–3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) CT-SPECT scintigraphy in our center as a sensitive, quantitative method for imaging transthyretin cardiac amyloid deposits. This bone scan tracer localizes with great affinity in all patients with cardiac transthyretin amyloid, and in a significant proportion of those with AL type, although the basis for this is not known.[3]

Ultimately, the diagnosis of amyloidosis must be supported by demonstration of amyloid in the tissues. While this can be achieved in specialist centers by means of serum amyloid P component (SAP) scintigraphy,[4] biopsy histology is accessible widely, and offers the means for identifying amyloid fibril type immunohistochemically or through laser capture microdissection and mass spectrometry, as described in Table 2 of Gertz and Dispenzieri’s review. In our own experience, immunohistochemistry is nondiagnostic in one-third of cases of AL amyloidosis, supporting the frequent need for mass spectrometry as back-up, although availability and turnaround times remain challenges for this sophisticated new technique. It is certainly not adequate to rely on the mere presence of a monoclonal gammapathy to confirm that amyloid deposits are AL type, considering that MGUS occurs in 5% to 8% of the elderly population,[5] and that wild-type transthyretin amyloid deposits are present at autopsy in 25% of individuals over 80 years of age.[6] Further, more than 5% of patients referred to our own center have hereditary types of amyloidosis, often with no family history.[7]

Our favorable recent experience of cardiac MRI and 99mTc-DPD scintigraphy has not eliminated a conundrum in some patients, which is applicable to the first case presented by Drs. Gertz and Dispenzieri. Is the amyloid detected peripherally in an abdominal fat aspirate necessarily the same type as that in the heart of an elderly patient? Senile cardiac amyloidosis has a better prognosis than AL amyloidosis and is not amenable to chemotherapy; it is vital not to subject an elderly MGUS patient with senile cardiac transthyretin amyloidosis to chemotherapy. At present, cardiac biopsy is
the only way to definitively distinguish cardiac transthyretin (TTR) from AL amyloidosis, and while
domyocardial biopsies must be performed selectively, we are optimistic that algorithms based on
some or all of the many cardiac investigations now available can be developed to provide guidance
in this area.

Much progress has been made in the treatment of AL amyloidosis in recent years. A search of
clinicaltrials.gov for AL amyloidosis identified 48 studies in the 15 years up to 2005 and 63 studies in
the 6 years since. In addition, the great unmet need in amyloidosis has gradually come to the
attention of the pharmaceutical industry. Rapid and substantial reduction in amyloidogenic free light
chain production can improve prognosis greatly. Amyloidogenic plasma cells appear to be
exceptionally sensitive to the apoptotic effects of proteosome inhibitors,[8] and early data suggest
that this translates into deeper clonal responses and more frequent and rapid organ responses in
patients treated with bortezomib.[9] Subcutaneous administration of bortezomib and newer
proteosome inhibitors with reduced toxicity may improve the treatment of patients with more
advanced disease. While there has been a mushrooming of novel agents and drug combinations in
myeloma, it will remain vital to identify therapies that produce responses in AL amyloidosis that are
rapid and as complete as possible. Amyloidotic organ responses, which depend on hematologic
response, may be very slow, and the combination of free light chain assays and measurement of
cardiac biomarkers provides crucial early information that can guide therapy remarkably effectively.
SAP scintigraphy is used routinely in the United Kingdom to serially track whole-body and organ
amyloid load, while new technologies, such as MRI quantification of the interstitial space occupied by
amyloid and possibly amyloid-specific agents for positron emission tomography (PET) are in
development.

Despite these developments, Drs. Gertz and Dispenzieri provide data from the Mayo Clinic over a
30-year period that show disappointing progress in treatment of patients with advanced disease,
with 30% to 40% of deaths still occurring during the first year. Treatments that directly target the
amyloid deposits are thus urgently required, and promising immunotherapy approaches are in
development.[10,11] Our own such approach utilizes antibodies to SAP,[11] a universal constituent
present in all amyloid deposits; these antibodies trigger near complete clearance of experimentally
induced amyloid deposits within 2 weeks.

Amyloidosis is moving into the mainstream, and growing interest from the pharmaceutical industry is
both welcome and exciting. However, despite much progress, late diagnosis and management of
advanced disease remain thorny challenges. At least they are ones that clinicians and researchers
are now vigorously addressing, offering new hope for patients with this grim disease.

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peptide in patients with light chain amyloidosis without cardiac involvement at presentation is a risk


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