

Contents

Preface: Shedding Tears to Clear the Way	xiii
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Raymond L. Comenzo

Introduction	xv
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Giampaolo Merlini

The Spectrum of Monoclonal Immunoglobulin-Associated Diseases	997
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Sascha A. Tuchman and Jeffrey A. Zonder

The spectrum of immunoglobulin paraprotein-associated diseases requiring therapy extends beyond multiple myeloma and AL amyloidosis. Awareness of these is essential in ensuring timely accurate diagnosis and appropriate treatment. As most paraprotein-associated diseases are fairly uncommon, therapeutic decisions must often be made in the absence of data from randomized controlled trials. Treatment is generally directed at the underlying clonal cell population. This review focuses on the spectrum of the less common paraprotein-associated disorders. In most instances, the monoclonal immunoglobulin plays a direct role in the pathophysiology of the disease course; in a select few, the paraprotein may be a disease marker.

Systemic Amyloidosis Due to Clonal Plasma Cell Diseases	1009
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Giada Bianchi and Shaji Kumar

Immunoglobulin light chain amyloidosis is the most common systemic amyloidosis. The pathogenetic mechanism is deposition of fibrils of misfolded immunoglobulin free light chains, more often lambda, typically produced by clonal plasma cells. Distinct Ig light chain variable region genotypes underlie most light chain amyloidosis and dictate tissue tropism. Light chain amyloidosis fibrils cause distortion of the histologic architecture and direct cytotoxicity, leading to rapidly progressive organ dysfunction and eventually patient demise. A high index of clinical suspicion with rapid tissue diagnosis and commencement of combinatorial, highly effective cytoreductive therapy is crucial to avoid irreversible organ damage and early mortality.

Systemic Amyloidosis due to Low-Grade Lymphoma	1027
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Ashutosh D. Wechalekar, Raj Chakraborty, and Suzanne Lentzsch

Lymphoma-related amyloidosis is a rare entity. Systemic AL amyloidosis is generally caused by an underlying plasma cell clone in the bone marrow with an intact monoclonal immunoglobulin G (IgG) or IgA protein. The rarity of the lymphoma-related amyloidosis makes the generation of data in randomized trials and the determination of the optimal treatment almost impossible. Therefore, treatment recommendations discussed here are based on either retrospective or small prospective trials of single centers.

The Process of Amyloid Formation due to Monoclonal Immunoglobulins 1041

Gareth J. Morgan and Jonathan S. Wall

Monoclonal antibodies secreted by clonally expanded plasma cells can form a range of pathologic aggregates including amyloid fibrils. The enormous diversity in the sequences of the involved light chains may be responsible for complexity of the disease. Nevertheless, important common features have been recognized. Two recent high-resolution structures of light chain fibrils show related but distinct conformations. The native structure of the light chains is lost when they are incorporated into the amyloid fibrils. The authors discuss the processes that lead to aggregation and describe how existing and emerging therapies aim to prevent aggregation or remove amyloid fibrils from tissues.

Systemic Amyloidosis due to Monoclonal Immunoglobulins: Cardiac Involvement 1055

Sunil E. Saith, Mathew S. Maurer, and Ayan R. Patel

Amyloid light chain amyloidosis (AL) is the most commonly diagnosed systemic form of amyloidosis, resulting from deposition of amyloid fibrils into various organs, such as the heart. Over the past several decades, significant advances in diagnosis and treatment have reduced overall mortality. Short-term survival, however, has not improved, in large part due to cardiovascular mortality from advanced AL cardiac amyloidosis. Early clinical suspicion of cardiac involvement is critical in order to initiate appropriate treatment and referrals for successful management. This review discusses the current challenges in diagnosis as well as available treatment options for different stages of cardiac involvement.

Renal Involvement in Systemic Amyloidosis Caused by Monoclonal Immunoglobulins 1069

Sabine Karam and Nelson Leung

Kidney involvement in immunoglobulin-related amyloidosis (Alg) is common. Although patients with renal-limited Alg tend not to have the high mortality that patients with cardiac amyloidosis have, they do experience significant morbidity and impact on quality of life. The complexity of the pathogenesis remains incompletely understood. Models have been established to prognosticate and assess for the response to therapy. Patients with advanced renal impairment from immunoglobulin light chain amyloidosis still have poor renal prognosis, and better therapy is needed in order to preserve kidney function. Patients who develop end-stage renal disease can undergo renal replacement therapy with kidney transplantation.

Liver and Gastrointestinal Involvement 1081

Michael Rosenzweig and Raymond L. Comenzo

Early diagnosis of AL amyloidosis and appreciation of the nutritional and coagulation abnormalities associated with liver and gastrointestinal involvement are critically important in the treatment and management. In cases of severe malabsorption total parenteral nutrition can be extremely helpful as a bridge to organ improvement. Rarely the use of antifibrinolytic agents such as oral aminocaproic acid with transfusion support may control severe bleeding in patients with coagulation abnormalities. It is

important to keep in mind that organ improvement should follow in lag phase after the reduction in the pathologic free light chain with treatment. Closely following light chain levels may permit brief holidays from treatment and enable periods of recovery before resuming therapy in patients with prompt early and deep hematologic responses.

Peripheral Nervous System Involvement 1091

Pariwat Thaisetthawatkul and P. James B. Dyck

Peripheral nervous system involvement in primary systemic amyloidosis is another important organ involvement in the spectrum of this disease entity. Early recognition may lead to an earlier diagnosis and treatment with improvement in prognosis.

Systemic Amyloidosis Caused by Monoclonal Immunoglobulins: Soft Tissue and Vascular Involvement 1099

James E. Hoffman, Naomi G. Dempsey, and Vaishali Sanchorawala

Clinical features of soft tissue amyloid light-chain (AL) amyloidosis include macroglossia, arthropathy, muscle pseudohypertrophy, skin plaques, and carpal tunnel syndrome. Vascular manifestations of AL amyloid include periorbital ecchymosis, jaw or limb claudication, and even myocardial infarction caused by occlusion of small vessel coronary arteries. Some of these features, such as macroglossia, periorbital ecchymosis, and the so-called shoulder-pad sign, are pathognomonic for AL amyloidosis. These findings may be the initial presenting features of the disease, and the recognition of these red flag symptoms is very important for the diagnosis and early intervention on the underlying plasma cell disease.

Options for Chemotherapy and Scoring Response and Relapse 1115

Cindy Varga and Chakra Chaulagain

Chemotherapy for amyloid light chain (AL) amyloidosis has evolved over the years. Although high-dose melphalan and stem cell transplantation remain the standard of care for eligible patients, a vast majority of the patients at the time of presentation are not eligible for this approach and require low-intensity but highly effective induction therapy, usually based on bortezomib. Immunomodulatory agents are not well tolerated, particularly by patients with AL amyloidosis cardiomyopathy, and are reserved for second-line or later therapy. Because there currently is no Food Drug and Administration–approved therapy, participation in well-designed clinical trials of high scientific merit should be considered.

Stem Cell Mobilization and Autologous Transplant for Immunoglobulin Light-Chain Amyloidosis 1133

Morie A. Gertz and Stefan Schonland

Stem cell transplantation was one of the first proven effective regimens for the management of immunoglobulin light-chain amyloidosis. Criteria for patient selection and the mobilization regimen become important features in ensuring a safe outcome. The technique of stem cell transplantation has evolved considerably in parallel with the development of new

Contents

chemotherapeutic agents for the management of amyloidosis. Optimal outcomes require both the use of effective novel agent induction and appropriate application of high-dose chemotherapy with subsequent stem cell reconstitution.

Monoclonal Antibody Therapies in Systemic Light-Chain Amyloidosis 1145

Amandeep Godara and Giovanni Palladini

In systemic light-chain amyloidosis, monoclonal antibodies target antigens that are either membrane-bound or circulating or deposited in the organs. CD38 holds high promise as a target against clonal plasma cells. Multiple anti-CD38 antibodies are either approved for use or being investigated in clinical trials. Daratumumab has been investigated and has clinical efficacy in upfront or refractory settings. High rates of hematologic response are seen with daratumumab, which translates to high organ response rates. Rituximab is usually integrated into the treatment regimen for IgM amyloidosis. Anti-amyloid therapies have shown preclinical proof of principle, but lack confirmation of improvement.

Solid Organ Transplantation 1161

Susan Bal and Heather J. Landau

Hematologic disease control combined with solid organ transplantation can result in long-term survival in selected patients with light chain (AL) amyloidosis and limited other organ involvement. Restoration of critical cardiac function with organ transplantation can render patients eligible for effective disease-directed therapies, including high-dose therapy and autologous stem cell transplantation. Access to directed-donor organs, exchange programs for renal transplantation, and extended-donor organs for cardiac transplantation improves the availability of organs for patients with AL amyloidosis. Disease recurrence in the graft and progression in other organs remain concerns but often can be managed with a variety of effective plasma cell-directed therapies.

Supportive Care for Patients with Systemic Light Chain Amyloidosis 1177

Sandy W. Wong and Teresa Fogaren

Light chain amyloidosis is a disease in which clonal plasma cells produce toxic immunoglobulin light chains that form amyloid fibrils with deposition in organs, most commonly the heart and kidneys, but also the nervous system, gastrointestinal tract, and soft tissues. Treatment directed at the clonal cells eliminates light chain production and further deposition and may enable organ improvement and decrease the risk of organ failure. Supportive care manages the symptoms of organ involvement and the side effects of treatment. Supportive care also addresses the psychological and social issues that may arise in patients with light chain amyloidosis.

The Impact of AL Amyloidosis: The Patient Experience 1193

Isabelle Lousada and Mackenzie Boedicker

This article focuses on the patient experience of AL amyloidosis; the unique challenges that patients face from the journey to diagnosis through

treatment; and management of this complex multisystemic disease. Included are descriptions of the most significant AL amyloidosis symptoms as well as addressing burden of disease, including financial concerns, and psychological impact. In 2015 a Patient Focused Drug Development meeting held at the Food and Drug Administration provided valuable data that is shaping the drug development landscape and are reviewed here. The article concludes with a list of useful resources and organizations for patients and caregivers.

Future Perspectives

1205

Angela Dispenzieri and Giampaolo Merlini

Opportunities and challenges in the field of systemic amyloidosis can be grouped into 4 categories. First, a deeper understanding of the pathogenesis of the disease is required. Second, a greater awareness of the disease, which will lead to an earlier diagnosis, is imperative. Third, end points for interventional trials are required to convey us to our fourth aspirations, which are novel therapies for patients with light chain amyloidosis.