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Update on AL Amyloidosis

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ABSTRACT

Early suspicion of AL amyloidosis requires taking a thorough personal and family history and holistic physical examination, particularly in patients with nephrotic range proteinuria, bilateral carpal tunnel syndrome, unexplained non-ischaemic cardiomyopathy, unexplained hepatomegaly, peripheral neuropathy, atypical multiple myeloma, monoclonal gammopathy of undetermined significance, and patient labelled as POMES syndrome should prompt urgent essential investigations including N terminal pro-BNP, troponin, twenty-four hours urine protein excretion, estimated GFR, Alkaline phosphatase, echocardiography, liver ultrasound, serum free light chain profile, serum and protein immune electrophoresis and immunofixation followed by prompt referral to haematologist for early diagnosis and timely treatment to improve survival and outcome for these patients especially when promising treatment became available.

Keywords

Amyloidosis, Heterogeneous organ dysfunction, Cardiomyopathy, Soft tissues.

Introduction

Light chain, or AL amyloidosis, is the most common form of primary systemic amyloidosis, with an estimated incidence of 10 cases per million worldwide [1,2]. It's a slowly progressive and insidious disease manifested by heterogeneous organ dysfunction or failure symptoms due to the deposition of insoluble fibrils arising from misfolded free light chains (FLCs). In decreasing order of frequency (between 75% to 5%), the affected organs are the heart and kidneys, followed by soft tissues, liver, peripheral and autonomic nervous system, and gastrointestinal system. Amyloidosis can also be localised in the urinary tract, lungs, trachea, skin, larynx, brain, and occasionally can present as bilateral carpel tunnel syndrome [3,4].

AL amyloidosis is considered a misfolding protein disease. AL amyloidosis develops due to monoclonal plasma cell dyscrasia in >90% of cases. It can develop in less than 10% from B cell neoplasm like chronic lymphocytic leukaemia, Waldenström macroglobulinemia, monoclonal gammopathy of undetermined significance (MGUS), or smouldering myeloma. About 10%-15% of patients diagnosed with multiple myeloma tend to have AL amyloidosis, and about 10% of AL amyloidosis patients have symptomatic multiple myeloma due to shared genetic risk factors [3]. Despite significant progress in the management of plasma cell disease, AL amyloidosis remains a real challenge in early diagnosis and treatment for clinicians across all practice settings.

Types of Most Common Amyloidosis

AL amyloidosis (primary) has Lambda immunoglobulin light

chain as a predominant precursor protein and accounts for 70% of AL amyloidosis, and Kappa light chains account for 20 to 25 %; AH Amyloidosis is caused by heavy chain immunoglobulin, AL/AH amyloidosis – a secondary disease to plasma cell disorder and is very rare. Normal and mutant Transthyretin (ATTR) related amyloidosis has been implicated in cardiomyopathy, carpal tunnel syndrome, and polyneuropathy. Amyloid A amyloidosis is most common in renal involvement. Additionally, there are rare hereditary amyloidosis types involving various precursor protein misfolding, e.g. Apolipoproteins, Gelsolin, Fibrinogen -alpha chain, Lysozyme.

Pathogenesis

Chromosomal translocation t(11;14) accounts for around 50% of AL amyloidosis and hypodiploidy in 10%. Minor B cell disorder causes clonality and fibrillogenic in the immunoglobulin light chain, which affects their stability. Thermodynamic and kinetic unstable light chain disrupts the tissue microenvironment, which leads to aggregation and formation of amyloidogenic misfolded protein and oligomers, which causes a wide spectrum of symptoms based on the type and degree of organ involvement. Symptomatic disease is preceded by hypersecretion of the light chain many years before; symptoms are vague and nonspecific, like fatigue, easy tiredness, shortness of breath and loss of weight [4]. This results in delaying the diagnosis and progression of organ dysfunction and ultimately irreversible and advanced organ failure [5].

Early recognition allows early diagnosis and prognostication, targeting the underlying clone, halting the abnormal fibril secretion, limiting the end-organ damage, potentially preventing fibril absorption, and increasing overall survival [6].

Cardiac involvement occurs in 70% of patients diagnosed with AL Amyloidosis, common manifestation are decompensated heart failure, atrial fibrillation, VT, VF,AV conduction delay or block, low voltage ECG, poor R wave progression in V1-V6, thromboembolic manifestation in the absence of AF due to left atrial myopathy as a result of infiltration with misfolded amyloidogenic light chain which leads to clot formation, misfolded amyloidogenic light chain can also trigger activation of P38 mitogen-protein kinase (MAPK) singling , leading to elevated level of reactive Oxygen spices and contributing to the transcription of pro-B-type natriuretic peptide (ProBNP) [6], Bradyarrhythmia commonly precede terminal cardiac events, severity of AL cardiac amyloidosis is the primary determinant of morbidity and mortality, classic signs of right heart failure may not be evident until cardiac disease is terminal and irreversible specially if the patient was treated symptomatically with diuretics before reaching the accurate diagnosis, differential diagnosis of AL cardiac amyloidosis are transthyretin amyloidosis which includes Wildtype non-hereditary amyloidosis (ATTRwt) previously was referred to as senile systemic amyloidosis because of the late onset of the disease), occasionally associated or preceded with carpal tunnel syndrome and spinal canal stenosis, diagnosis can be confirmed with cardiac biopsy, technetium-99m-3.3-diphosphonate [1,2].

Propandicarboxylic acid (99m TC-DPD) Scan is a valuable tool for the diagnosis. Another type of cardiac amyloidosis which needs to be ruled out is hereditary Transthyretin amyloidosis, which is usually associated with small fibre, length-dependent and autonomic neuropathy, heart valve involvement leading to valve incompetence is common,

Other organ involvement includes myopathy, leptomeningeal amyloidosis, keratoconjunctivitis sicca, nephrotic syndrome, progressive renal failure, diarrhoea, malabsorption, hepatomegaly and elevation of alkaline phosphatase. Disease has two peaks: early and late-onset disease. A molecular test for the TTR gene is the gold standard for reaching an early diagnosis and timely management [7,8].

AL Amyloidosis can also affect the kidney, causing nephrotic range proteinuria, predominately albuminuria, elevated creatinine, hyperlipidaemia, hypoalbuminemia, and arterial and venous thrombosis [9,10]. AL Amyloidosis affects the nervous system in 15 to 20%, causing orthostatic hypotension, bladder and bowel dysfunction, spinal canal stenosis, mixed sensory and motor neuropathy, Other organs can be affected, like the liver, causing hepatomegaly, liver cirrhosis, portal hypertension, and liver rupture [9]. Pulmonary involvement includes pleural effusion, diffuse alveolar septal and tracheobronchial disease, soft tissue disease, including periorbital purpura, macroglossia, obstructive sleep apnoea, and carpal tunnel syndrome [11].

Every patient with bilateral carpal tunnel syndrome, peripheral and autonomic neuropathy, nephrotic proteinuria, hepatomegaly without imaging abnormalities, macroglossia, and periorbital ecchymosis should be investigated for amyloidosis. A high index of suspicion is paramount to prevent any delay in the diagnosis [12]. Confirmation of the diagnosis requires evidence of amyloidogenic misfolded fibril in a target or surrogate organ and evidence of plasma cell dyscrasia. Abdominal fat, lip, bone marrow, and rectum are considered good-yielding surrogate organs,

Evaluation for every patient for monoclonal gammopathy of undetermined significance and monoclonal gammopathy of renal significance should be the first step once clinical suspicion for systemic amyloidosis in any patient presenting with suggestive symptoms and signs. The workup includes serum and urine immunoelectrophoresis, serum free light chain, serum and urine immunofixation, twenty-four urine protein excretion, serum creatinine, NT-proBNP, troponin, alkaline phosphatase, echocardiogram, cardiac MRI if available. If MGUS is ruled out, AL amyloidosis is unlikely, and other types of amyloidosis should be considered with other investigations like PYP scan, DNA testing and target organ biopsy, If MGUS is confirmed, the patient should have a target or surrogate organ biopsy with Congo-red staining and fibril typing. A combination of abdominal fat and bone marrow biopsy is very safe and has a sensitivity and specificity of up to 90%. If a surrogate biopsy proves negative for amyloidosis, a target biopsy is advised if there is still high clinical suspicion. Once amyloid is detected, the typing of the fibril should be determined

by immunohistochemistry, immunofluorescence and a laser microdissection with mass spectrometry-based proteomic analysis [13,14], which many organisations consider the gold standard.

Elevated cardiac markers, low voltage ECG, decreased global left ventricular strain. Increased thickening of the left ventricular wall and interventricular septum strongly suggests cardiac AL amyloidosis. Positive 99m Tc-PYP scan in the absence of abnormal serum free light chain ratio almost wholly rules out AL cardiac amyloidosis and confirms transthyretin (ATTR) cardiac amyloidosis. Cardiac biopsy is rarely indicated where there is suspicion of ATTR with monoclonal gammopathy of undetermined significance or nonclassical presentation of dilated cardiomyopathy [10].

Risk Stratification

Risk stratification differs among organisations, but Mayo's 2012 model is the most common [9]. That assigns a score of 1 for troponin T>0.025ug/l, NT-ProBNP>1800ng/l, or BNP>400ng/L.

Differences in serum Free light chain between involved and non-involved free light chain(dFLC>180mg/L) are considered very high risk. Cardiac involvement predicts a high risk for mortalities. Other predictors include age, performance status, comorbidities, high-risk cytogenetics, plasma cell burden, high proteinuria, and low estimated GFR [14].

Treatment

All newly diagnosed patients will go for disease-directed therapy according to recently published **phase 3 ANDROMEDA**.

Daratumumab, cyclophosphamide, bortezomib and dexamethasone (Dara+CyBorD treatment)

Daratumumab is a monoclonal antibody of human immunoglobulin Gκ (IgGκ). The clonal plasma cells express CD38 -the target for DARA in addition to a direct on-tumor and immunomodulatory mechanism of action [12]. This treatment regimen eradicates and halts the production of amyloidogenic lymphoproliferative clones and the production of amyloidogenic fibrils. Patients should also be evaluated for autologous stem cell transplant (ASCT). Patients who achieve good partial response (VGPR)- defined as dFLC (measurable difference between involved and uninvolved FLC) less than 40 mg /L after four cycles of DARA SC-CyBorD, should be offered autologous stem cell transplant and daratumumab for a total of two years.

If patients do not achieve a very good partial response but achieve a partial response (reduction in dFLC by >50%) instead, patients should be given an additional two cycles followed by ASCT. Favourable factors for consolidation therapy and autologous stem cell transplant are young age, only kidney involvement and eligibility for a kidney transplant, or AL and multiple myeloma overlap. Second-line treatment could be considered in the absence of very good or partial haematological response [14].

Treatment Response and Follow-up Measurements

Amyloidosis CR (aCR) criteria require normalisation of FLC levels and ratio and negative serum and urine immunofixation (IFE).

The haematological response is measured based on decreased serum clonal immunoglobulin and serum free light chain level. dFLC> 10mg/l in patients with baseline dFLC between 20 and 30 is associated with significant overall survival and reduced risk of dialysis.

Organ responses for the heart, kidney, and liver are measured by the level of NT-Pro-BNP (>300ng/L reduction in NT-ProBNP), proteinuria (at least a 30% reduction in proteinuria), and Alkaline phosphatase, respectively. Patients should be assessed for haematological response every three months after ASCT and every three and six months after the initiation of therapy. Patients who did not receive ASCT should be evaluated every three months for the first year and then spaced. There is no approved treatment yet by the US FDA for relapsed or difficult-to-treat AL Amyloidosis.

Potential options for relapsed patients might be the same first line of treatment if the first response lasts more than one year. The other options are proteasome inhibitors, Anti CD38 monoclonal antibodies, Venetoclax (VEN) - a BCL-2 inhibitor, is promising as a treatment on its own or in combination with dexamethasone or other plasma-cell directed agents for patients with the translocation between the chromosomes 11 and 14 (t[11;14]) PCD [13].

Antifibril Monoclonal Antibodies (e.g. Trials with Birtamimab and Anselamimab)

Chemotherapy for AL Amyloidosis targets plasma cell neoplasm and amyloidogenic fibril, but it does not affect amyloid deposits in tissues. Two anti-fibril antibodies are currently being investigated, which can potentially remove amyloid fibril from organs by activating the immune system and degrading it by inducing antibody-dependent phagocytosis.

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