Primary Systemic Amyloidosis

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ABSTRACT

Amyloidosis AL is a disease which is caused by abnormal production of protein and accumulation at body organs. It causes pathological change and alters organ function especially in vital organs that can initiate fatal complications. The causes are idiopathic or acquired from multiple myeloma. Early diagnosis and prompt immediate treatment is the best way to prevent vital organ involvement. However, the clinical manifestations are heterogenous and not specific which means the diagnosis is not met at the first visit. Consideration of its conditions is basically to find out early signs of the disease. The treatments are based on the performance status of patients and impairment of some organs and aims to provide suitable care such as chemotherapy, immune suppressive drugs or transplantation of stem cells.

Keyword: Amyloidosis

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Amyloidosis is a syndrome which has abnormal amounts of natural human protein named amyloid pathologically stored in extra cellular components of body organ. Amyloid light chain (AL) is the most frequent type of acquired amyloidosis. There was a report by the American association of hematology that its frequency by age-adjusted incidence was 5.1-12.8 per million a year.[1] This disorder was estimated to find 10-15% associated with multiple myeloma.[2] For kidney involvement, there was a review about it in Thailand which found 2.1% from 1,000 kidney biopsies over 20 years.[3] AL produces monoclonal immunoglobulins that are precursors of amyloid fibrils and occurrs mostly in the elderly.

Natural history

AL commonly has extensive systemic involvement. Cardiac abnormality was found about 90% as congestive heart failure (CHF) and cardiomyopathy about 30%. Half of the patients died by coronary heart disease, arrhythmia and bradycardia. EKG may show pseudo-infarction and an echocardiogram may detect thickness of the cardiac wall. Kidney involvement initiates with proteinuria and will progress to be nephritic syndrome. Ten percent of patients who have nephritis without diabetes may have amyloidosis. Gastrointestinal (GI) association produces abnormality of dysmotility by autonomic neuropathy, malabsorption, gut wall perforation, GI hemorrhage or gut obstruction. Fifteen percent of patients were reported to have hepatomegaly with high alkaline phosphatase which might involve splenomegaly. Neurological complications occurred as peripheral neuropathy in 20% of cases. The most is sensory neuritis. Axonal and demyelinating processes are also the causes of this disorder and firstly affect at the longer nerve of the legs preceding the diagnosis of amyloidosis. Carpal tunnel syndrome was found in half of these patients. Autonomic neural dysfunction apart from GI dysmotility also has some clinical manifestations such as orthostatic hypotension or impotence. In the brain, demyelinating processes lead to cortical defect, dementia and changing cerebral vessel risky to a cerebrovascular accident. It can present with a skin rash, small tag at the trunk or face and a specific pink rash under both eyes. Macroglossia was rarely reported, but specific for diagnosis. Patients may have joint involvement showing as polyarthritis which can mimic as rheumatoid arthritis. Glenohumeral joint involvement was found with a shoulder pad sign that was pathognomonic feature. The patients may have bruising and ecchymosis. Bleeding tendency was rarely reported, but was often severe when it occurred. Amyloid can absorb factor X^4 to make its level lower and also factor IX. Bleeding tendency was recorded only in AL with one report which demonstrated that half of the patients have coagulopathy and 28% have bleeding.[5] Bleeding could also be precipitated with vessel impairment from amyloid deposit[6] or von Willebrand disease. Complications of the respiratory tract can present with a bronchial and laryngeal mass resulting in dyspnea, hoarseness and stridor in 1-2% of cases.[7] Pleural effusions may be associated with CHF and was

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associated with poor prognosis.[8,9] Because of the variation and ambiguity of symptoms, the patients may be found with indefinite symptoms to completely clearly diagnose. The physician must recognize these symptoms especially in cases of non diabetic nephritic syndrome, heart disorder in young people who have less vascular risk or disorders that are found with multiple systems involvement.

Investigations

Monoclonal paraproteins cannot usually be found by electrophoresis. The method which should be used instead is immunofixation[10] which was reported with 90% sensitivity. The remainder who are still not detected by immunofixation, can be additionally checked by free light chain nephelometric assay[11,12] to reevaluate and detect 75% of cases. It can be used to follow the response of treatments and point out amyloidosis as AL subtype. Tissue pathology can be applied according to site involvement. Bone marrow (BM) and subcutaneous fat biopsy have importance to diagnose by performing congo red staining and viewing under polarizing microscopy. This will show apple green birefringence with sensitivity 57-85% and specificity 92-100 %.[13] The concordance of BM and subcutaneous fat demonstrates the probability of amyloidosis in 62% of cases. Rectal biopsy has more sensitivity at 84% than either of BM or subcutaneous fat. Liver, kidney and carpal tunnel biopsy may have sensitivity of 90% or more, but is difficult to biopsy. The pathology of amyloidosis shows as amorphous hyaline material under light microscope and by electron microscope as a non branching straight line about 8-10 nanometers long.[14] Immunohistology has a benefit to discriminate the types that do not relate to immunoglobulins. In addition to basic detecting, monitoring heart involvement is mentioned; stain echocardiography has more sensitivity than normal echocardiography.[15] Follow up echocardiography every 6 months in affected cases by testing of the ejection fraction and thickness of interseptal heart walls is recommended. CHF if it occurs can be used to predict survival as not longer than 6 months and doppler echocardiography if it detects a diastolic period of the heart longer than 150 ms can predict one year survival in only 50% of cases. However, change in the infiltrated organ usually has slow progression and it is difficult to decide the suitable interval time for follow up investigations. Different schedules of each institution are problems to establish consensus. Technetium scan can be used for evaluation of cardiac status.[16] Magnetic resonance imaging (MRI) is a tool to distinguish ventricular hypertrophy caused by amyloidosis apart from hypertension.[17] β_2-microglobulin has been proposed as poor prognosis if more than 2.7 μg/ml are labeled.[18] Troponin T helps as an indicator of survival and monitors the clinical course. There was a previous report which reviewed the median survival of 6 and 22 months between negative and positive results in cardiac involvement.[19] NT-pro BNP produced by a dilated cardiac chamber is another sensitive test and a good predictor.[20,21] If its level was more than 152 pmol/L, survival was poorer than the lower leveled group. Reduction of Troponin T was found to correlate with lowering of free light chain as demonstration of organ response after treatments.[22,23] NT-pro BNP and troponin T are now established as the new staging system to classify amyloid involved cardiac patients by a critical level of NT-pro BNP at 332 ng/L troponin T 0.035 μg/ml and troponin I 0.1 μg/ml.[21] The patients are divided into three groups. The first is the group with NT-pro BNP values below these thresholds with the remainder of any one also below. The second is the group having a value lower than a threshold value only and finally all are more values above the criteria. There was a relative median survival of 26-27 months, 10-11 months and 3.5-4 months, for each group. This system can be used to predict in all new cases and after treatment and now includes uric acid at more than 8 mg/dL to be an additional risk factor.[24]

Treatments: AL

Amyloidosis must be discriminated by each type apart from AL because of resistance of chemotherapy (CT) and stem cell transplantation (SCT) of those types. The main principle is to decrease the precursor of amyloid that have which is benefited by CT. Its rareness makes general physicians to have not experience to diagnose this disease and provide treatment. Because of these, AL treatment is specifically reviewed in this section. The effective treatment of AL is to early diagnose and promptly treat on time with least amyloid induced damage. Selected type of treatments would be weighed among efficacy, availability of patients and physical condition. The response will be indicated by the better function of organs. The most effective treatment is high-dose melphalan (HDM) and then peripheral blood autologous SCT which is an important treatment in myeloma patients with amyloidosis. This treatment has been used since 1996 CE but had high treatment related mortality (TRM) for nearly half of the patients. There was a further classification to choose patients to be grouped for different treatments according to patient age, number organ involvement and cardiac involvement. Good risk was defined as less than 2 organ involvement without cardiac involvement and creatinine clearance (CrCl) more than 51 mL/min. Younger patients less than 60 years could be treated with HDM at 200 mg/m^2 and in descending order, respectively, when age increased. It could be used in the elderlys more than 71 years. Intermediate risk was defined as a group of worse renal function and subclinical or compensated cardiac involvement. They decreased melphalan (mel) in age of 60 years at 140 mg/m^2 and when the age increased. It should be treated until patients are aged less than 70 years. For patients with cardiac involvement, SCT was definitely not recommended.[25] Another institution established criteria including ejection fraction (EF), systolic blood pressure (SBP), O2 saturation (Sat) and performance status (PS) more than previously. SCT could be used to treat sequentially with mel in patients younger less than 65 years with EF> 0.45, SBP> 90 mmHg, Sat >95% and good PS. They would receive mel 200 mg/m^2, but in the older aged person not more than 80 years and EF> 0.40 or less stem cell collection received mel 140 mg/m^2. Other patients who should not be recommended for SCT are those who have pleural effusion.[26] Because of HDM, there is a risk with SCT at 15%, so a less toxic conditioning regimen, VAD (Vincristin, Adriamycin, and high dose dexamethasone) is used instead. Tandem SCT can also be useful in patients for whom the first response is not satisfactory. After 3 months of SCT which is not successful, more treatments need to be added. TRM was reported about

13-20% with about a half of patients having complications resulting from the heart.[26] GI complications also occurred with more than grade 2 of nausea, vomiting and mucositis in 46% of cases. Peripheral edema, renal insufficiency and septicemia were found as about 19, 18, 16%, relatively.[27] Renal impairment could be improved in a half after the end of treatment. There were risk factors of treatment as renal status, cardiac status, complicated infection and dose of mel which was used.[28,29] Currently, TRM has been lower due to better supportive treatment below 10%. SCT was also useful in patients older than 65 years. The complications of treatment, disease response and survival were not different from the younger patients.[30] Patients still had the risk of complicating infection after SCT for 6 months. The overall response (OR) was about 50-60% with complete response (CR) 14-36% and organ response 34-55%.[26] By increasing the dose of mel results in a more critical response. Response was very different according to organ. Kidney, liver, heart, nervous system and GI were consequently responsive. SCT resulted significantly better survival compared with previous alkylating based CT.[31] In the cases of poor response as still having abnormal clonal plasma cell after 3 months of SCT, it would be maintained with thalidomide (thal) and dexamethasone (dexa), later 9 months after that, there was CR 36%, partial response (PR) 71% and OR 44% with a 2 year survival of 84% and TRM 4.4%.[32] However, the report also found the opposite result as SCT might not have better results than other treatments in patients with good risk.[33,34] Another randomized trail supported that survival of SCT not much more than mel and dexa.[35] However, there was an argument that this study had more TRM at 24% and included patients who also had more organ and cardiac involvement. Therefore, current recommendations are still that, for patients who are suitable and strong enough, SCT is also the best first-line treatment. Allogeneic cell would lead to a graft versus plasma cell dyscrasia effect in AL patients.[36,37] One study of SCT demonstrated in 15 patients, in which a half had CR and only one had recurrence after 31 months. Free light chain assay was established as the good monitor to follow response. Patients, who had no response to CT, had still benefited from SCT according to the immunologic effect. However, TRM was still highly related to poor PS and total body irradiation (TBI).[37] The same as other leukemias, a reduced intensification conditional regimen had less mortality than a conventional regimen.[38]

For patients who cannot tolerate to SCT, CT is still a relatively standard treatment. The first is mel that has been reported to be potent for a 10 year survival with only a standard drug dose and not even CR.[39] There was OR 28% with 30% of responsive cases longer than 1 year. Mel may precipitate acquired genetic mutation leading to acute leukemia in 20% within 3.5 years after receipt.[40] This drug has been limited in patients who had already renal insufficiency and produced slow response of the disease. Now, it is replaced by other more effective drugs. There was also a report that found benefits of it to use mel in patients with heart failure.[41] Mel as pulse therapy combined with dexa is the first line drug in patients who are not candidates for SCT with CR 33% overall response rate (ORR) 67%.[42] This therapy was reported as time to response about 4 mouths and mel/prednisolone was even longer about 7-11 months. There was median progression free survival (PFS) 3.8 years, overall survival (OS) 5.1 years[43] and TRM 4%. The faster responsive combination, VAD as used in myeloma may have some complications in amyloidosis patients such as more toxicity of neuropathy from vincristin, and cardiac complication from doxorubicin. Dexa usage also has more cardiac congestion. However, there were some studies about this regimen which demonstrated to have a clonal response of 50% with TRM 7% by most of the included patients who had no cardiac and neurological involvement. Twenty five percent of those who had response would have recurrent disease within 2 years.[44] Only high dose dexa is able to be responsive, but various numbers of responses have been reported from each study. The schedule that was used in VAD had TRM 7% as that original VAD regimen did. The modified dose was one third who still had OR 35% within 4 months without any complications, but no response in cardiac involved patients. There was one report using dexa as a schedule in a VAD regimen combined with interferon α for 2 years and then cont inue interferon alone for a further 3 years. It had OR 45% and OS 60% with many complications even TRM 7%.[45] The next drug can be used; thal which has relative intolerant side effects has been reported to produce good response. It may be initiated in lower doses increasing to maximum 400 mg per day and used in combination with high dose dexa.[46] This combination has always been used in resistant or refractory to treatment cases with OR 48% and CR 19%. Response of disease with thal was found to predict survival significantly but with high side effects as 65%, one fourth with bradycardia. To relief side effects, diminishments of the thal dose to 200 mg per day had still more side effects in 62% of cases.[47] Cyclophosphamide was used to add in the thal/dexa regimen to be potent as CR 21%, ORR 73% and 3 years survival of responsive patients was 82-100%. However, there was level 2 of side effects in a half of cases and needed to decrease the dose in one third.[48] Lenalidomide, a related compound of thal which has more potency than thal as high as 100 times with less toxicity, was used as a single agent or combination with dexa with production of ORR 67-75% and OR 42%.[49,50] Up to date, thal and lenalidomide have still been studied in recurrent or refractory to treatment cases. Bortezomib, the proteosome inhibitor, has been studied in a wider range of conditions as the first line regimen for refractory cases and in combination with a conditioning regimen before SCT. It was tested to be used singly and in combination with dexa. ORR found at 71% within nearly 2 months with CR of 25%. Naïve patients had a 47% CR rate. Twenty nine percent of patients had cardiac response. Toxicity was the same as thal but less and manageable.[51] 4-iodo-4-deoxydoxorubicin (IDOX) can resolve accumulation of amyloid especially AA subtype. It also demonstrated such effects with AL, but only in a small and unreliable study.[52] Immunotherapy such as vaccine and antibody are currently being studied more with limited clinical efficacy now.

CONCLUSION

It is importance to be aware for these disorders which always have many characteristics of symptoms to

confuse with similar conditions that cause other diseases. Delay of diagnosis leads to inappropriate treatment in time and pathological and irreversible changes that cannot be solved much later. Rareness of affected cases makes for lack of expertise and understanding of general practitioners and non-specialist physicians. They must recognize and can learn more with this review. These are innovative therapies and better supportive treatment can be used to improve patient conditions caused by new molecular and genetic information. Prevention of disease complications with diminishment of amyloidosis is the better way to treat these patients.

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