Nonfamilial systemic amyloidosis: a case study of a Medicine Department

Margarida Ascensão*, Helena Figueiredo**, José Pontes***, Ana Paiva****, Paula Pimenta**, Francisco Parente**, José Feio*****, Borges Alexandrino******, Políbio Serra e Silva*******

Abstract

The authors present the causes of non-familial systemic amyloidosis seen in a department of Internal Medicine. The work includes 21 patients with a diagnosis of amyloidosis. The diagnostic distribution varied between primary (AL), secondary (AA) and b_2 – microglobulin (b_2M). The study group was comprised of 13 on women (62%) and 8 men (38%) with an average age of 61.5 years (min. 31/max.85).

In this group the authors studied some aspects which highlight the causes leading to the investigation of amyloidosis, the associated pathologies, the clinical-laboratorial syndromes the distribution of the several types of amyloidosis, the biopsy locations, the evolution of the diseases and the patients survival.

Key words: systemic amyloidosis, potassium permanganate test, classification, diagnosis, clinical manifestations.

Introduction

The term "amyloidosis" refers to a group of conditions characterized by the deposition of abnormal protein material in the extracellular tissue, resulting from a change in the protein metabolism and leading to disruption of the tissue structure and loss of the normal tissue elements.

The etiology and pathophysiological mechanisms that lead to this deposition are not very clear, and appear to differ depending on the type of amyloidosis in question.[1] These proteins, which are variable on the peptide subunits that compose the fibrils, share common physical and chemical properties and characteristics such as green birefringence under polarized light after Congo Red staining and b-pleated structure determined by X-ray diffraction.

Several classifications of amyloidosis have been defined: primary or secondary, hereditary or acquired, localized or systemic. More recently, with the development of immunocytochemical techniques that enable the identification and distinction of the proteins that constitute the fibrils involved in the different clinical syndromes, a new nomenclature and classification was adopted (established in Oslo by Husby in 1990[2] — *Table 1*). The various clinical syndromes of acquired amyloidosis identified to date, and their respective protein fibrils and precursors involved, are shown.

In addition to these variable fibrils, constituting their major subunits (approximately 90%), the amyloid substance is also composed of a non-fibrillar glycoprotein, component P (10 to 15%).[3,4,5,6] Component P, which is present in all types of amyloidosis, except intracerebral amyloidosis, derives from a normal serum precursor (SAP – Serum Amyloid P Component) related to an acute-phase reactive agent (C-reactive protein).[3,4,5] Its function is not yet well--defined; it seems to interact with the deposited fibrils, protecting them from proteolytic digestion,[6] and it may therefore be responsible for the irreversibility (today this is deemed as an absolute statement) and poor prognosis of this disease.

Glycosaminoglycans and the "amyloid-enhancing factor" are also common components of the amyloid substance. Their role in the amyloidogenic process is not yet completely known.[4]

Some of the major clinical types of amyloidosis are briefly described below. They differ from each other

*Resident to the Internal Medicine Supplementary Internship

**Internal Medicine Hospital Assistant

***Gastroenterology Hospital Assistant

****Resident to the Nephrology Supplementary Internship

*****Hospital Pharmacist

******Senior Assistant in Internal Medicine

*******Head of Service

#Work presented at the XIII Jornadas de Medicina Interna do Porto (Porto, 16 to 18 November 1994) and at the XIII Jornadas de Medicina Interna de Coimbra (Coimbra, 3 and 4 February 1995)

Medicine Services II of the Hospitais da Universidade de Coimbra

Received for publication on the 3rd January 1997

TABLE I

Classification of acquired systemic amyloidosis

Clinical syndromes	Protein fibrils
Systemic AL amyloidosis associated with immunocyte dyscrasias, myeloma, MG, occult dyscrasia	AL fibrils derived from monoclonal immunoglobulin light chains
Localized nodular AL amyloidosis (skin, respiratory tract, urogenital tract, etc.) associated with focal immunocyte dyscrasia	AL fibrils derived from monoclonal immunoglobulin light chains
Reactive systemic AA amyloidosis associated with chronic active diseases	AA fibrils derived from serum amyloid A protein (SAA)
Senile systemic amyloidosis	Transthyretin derived from plasma transthyretin (TTR)
Focal senile amyloidosis	
Atrium	Atrial natriuretic peptide
Brain	β-protein
Joints	not yet characterized
Seminal vesicles	not yet characterized
Prostate	β_2-microglobulin
Alzheimer's disease, dementia in Down's syndrome, cerebral amyloid angiopathy	β-protein derived from a beta-amyloid protein precursor (APP)
Creutzfeldt-Jakob disease, kuru (transmissible spongiform encephalopathies, prion diseases)	Prion protein (PrP) derived from the prion precursor
Diabetes mellitus type II	Islet amyloid polypeptide (IAPP), amylin, derived from its protein precursor
Endocrine amyloidosis associated with "APUDomas"	Hormones or peptide fragments (e.g., pre-calcitonin in medullary thyroid carcinoma)
Amyloidosis associated with haemodialysis (osteoarticular or systemic)	β_2-microglobulin derived from high plasma levels
Primary localized cutaneous amyloidosis	Possibly derived from keratin
Ocular amyloidosis (corneal, conjunctiva)	not yet characterized

Adapted from Bergsagel and Kyle[12]

not only in the fact that they involve different proteins, but also in their different forms of presentation.

Secondary amyloidosis, reactive systemic amyloidosis or AA amyloidosis

In this type of amyloidosis, the fibrillar protein deposited in the tissues is the amyloid A protein, which is also found in a hereditary-familial condition - familial Mediterranean fever. By definition, this type of amyloidosis occurs in association with other diseases: infectious, inflammatory or neoplastic disease (*Table 2*).[7] The average age at the time of diagnosis is 51 years for males and 64 for females.[8] In the pre-antibiotic era, associated diseases were the most frequent causes of amyloidosis, but their spectrum has changed dramatically, now representing only 5% of the causes of systemic amyloidosis in industrialized countries (*Fig. 1*).[9] Currently, the most frequent causes of secondary amyloidosis are prolonged rheumatic diseases (mean duration of 19 years), and of these, rheumatoid arthritis in 75% of the cases (two thirds).

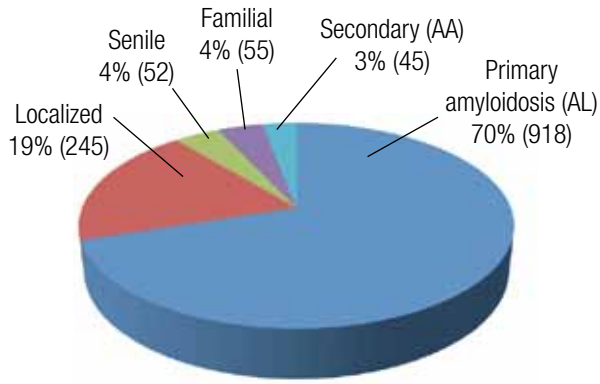
The amyloid A protein derives from an acute-phase

TABLE II

Diseases associated with secondary amyloidosis

Autoimmune diseases	**Malignant diseases**
Rheumatoid arthritis	Hypernephroma
Ankylosing spondylitis	Hodgkin's disease
Behçet's syndrome	Melanoma
Gout	Solid digestive
Vasculitis	Pulmonary or genitourinary tumors
Sjögren's syndrome	Other lymphomas
Polymyalgia rheumatica	**Others**
Inflammatory bowel disease	Diabetes mellitus
Infections	Paraplegia
Tuberculosis	Cystic fibrosis
Leprosy	Drug addiction
Schistosomiasis	Bronchiectasis
Osteomyelitis	
Empyema	

Adapted from Vogelgesang and Klipple[7]



Adapted from Kyle & Gertz

Types of amyloidosis in 1315 patients (1981-1992).

FIG. 1

protein – serum amyloid A (SAA). Its function is still unknown, and high levels of SAA have been found in patients with secondary amyloidosis.[6,10]

Classically, proteins are deposited on the parenchymal organs, frequently on the renal tubular basement membrane and subcutaneous fat.[11]

Clinically, the most common form of presentation results in renal involvement, and the presence of hepatosplenomegaly is also common. The heart and gastrointestinal tracts can also be involved, but their functions are rarely changed.[12]

Primary amyloidosis associated with immunocyte dyscrasias, or AL

In this type, the amyloid fibrils derive from monoclonal immunoglobulin light chains (light-chain amyloid protein), mostly resulting from the proliferation of a B-cell clone. It occurs in the absence of infection, inflammation, hereditary disease or neoplasm (excluding multiple myeloma).

It may be idiopathic or associated with multiple myeloma (5% to 15% of patients with primary amyloidosis), Waldenstrom's macroglobulinaemia or agammaglobulinaemia.[7,12]

Histologically, although it can involve any tissue or organ, there seems to be a tendency for nodular deposition and involvement of small blood vessels.[11]

Most patients have monoclonal gammopathy (MG) in the serum or urine (85%). The organs most often involved are the heart (90% of the cases), kidney, digestive tract, peripheral nervous system (PNS) (20% of the cases) and the carpal ligament, autonomic nervous system, skin, muscles and joints, and clotting factors.

Of all the forms, this is the most common (*Fig. 1*), and the one with the poorest prognosis.[11,13] Its incidence is 8.9 in 10 millions/year, mean age of 62 years, rarely occurring before 40 years of age.[8,14]

Familial or hereditary amyloidosis

It is usually autosomal dominant, except for familial Mediterranean fever, which is autosomal recessive. Most amyloid fibrils of this type are transthyretin (TTR).

The neuropathic forms usually manifest as peripheral sensory neuropathy and autonomic neuropathy. Other forms include the familial nephropathic form, the cardiac form and others. These forms were excluded from our case series.

Amyloidosis associated with haemodialysis

The protein found in this type of amyloidosis is b_2-microglobulin (b_2M), and as the name suggests, it occurs in haemodialysis patients, usually five years after the beginning of treatment.[7]

It usually involves the joints and periarticular

TABLE III

Biopsies for the identification of amyloid substance

Identified sites	Positive (%)	Negative
Autopsy	1	—
Abdominal subcutaneous fat (asp)	—	2
Abdominal subcutaneous fat (biop)	15 (94)	1
Rectum	2 (50)	2
Kidney	—	1
Liver	1 (33)	2
Skin	3 (60)	2
Carpal annular ligament	1 (100)	—
Nerve, muscle, enlarged lymph nodes	1 each	—
Lung, small intestine	—	1 each

structures, and the carpal tunnel is often affected.

Below, we present a case series from the Department of Medicine II of Coimbra University Hospitals relating to nonfamilial systemic amyloidosis.

Material and methods

This study carried out a retrospective evaluation of all cases of nonfamilial systemic amyloidosis treated at the Department of Medicine II of HUC between 1985 and 1994.

All patients were included who presented a systemic clinical condition compatible with amyloidosis, and an anatomopathological substance identifying an amyloid substance. All cases of familial amyloidosis were previously excluded. For the selection of patients, we relied on previously studied clinical cases with specific characteristics and a previous study on biopsy of abdominal fat conducted at our Department, from which we selected patients with positive biopsy.

Our sample consisted of 21 patients – thirteen females and eight males. The average age was 61.5 years, ranging from 31 to 85 at the time of diagnosis.

Of these patients, we excluded one published case[15] of B_2M amyloidosis because it involved a less common form of presentation in this type of amyloidosis. It was the case of a male patient, 31 years, insulin-dependent diabetic, with chronic renal insufficiency and on haemodialysis for 5 years. Clinically, the patient had bilateral parotid hypertrophy, macroglossia, peripheral polyneuropathy and a condition of superior vena cava syndrome. The amyloid substance was detected by biopsy of the abdominal fat, and the immunocytochemistry characterization was compatible with the b_2M type. Thus, systemic involvement and positivity for biopsy of abdominal fat were observed, which is rare in this disease.

The remaining 20 patients were analyzed simultaneously, according to some parameters: sites where the amyloid substance was identified, clinical syndromes present, associated pathologies, echocardiographic changes, plasmacytosis, immunoelectrophoresis, criteria for differential diagnosis between primary and secondary amyloidosis (clinical criteria - organ distribution, underlying etiologies, presence of MG, and echocardiographic changes — and permanganate test), survival and causes of death.

Results

The amyloid substances of the 20 patients were analyzed; the analysis was positive on three sites tested for 1 patient, two sites for 4 patients, one site for 14 patients, and autopsy was performed in 1 patient.

Biopsies were performed on: the abdominal subcutaneous fat (by puncture, aspiration or biopsy), rectum, kidney, liver, skin, annular ligament, nerve, muscle, enlarged lymph nodes, lung and small intestine. The results are presented in *Table 3*.

The clinical conditions of these patients were as follows (*Table 4*): symptoms in the heart region in 12 patients (60%), congestive heart failure in five (25%), renal insufficiency in seven (35%), nephrotic syndrome in three (15%), non-nephrotic proteinuria in six (30%), peripheral polyneuropathy in six (30%), carpal tunnel syndrome in four (20%), skin manifestations (purpura and subcutaneous infiltrate) in four (20%), gastrointestinal symptoms (diarrhoea/obstipation/malabsorption) in five (25%), macroglossia in two (10%), orthostatic hypotension in three (15%), adenopathy in four (20%), hepatosplenomegaly in one, goiter in one, and factor X deficiency in 2 of 4 patients analyzed.

In this case series, the some patients presented association with other pathologies, especially chronic pyelonephritis and diabetes mellitus, which was present in three patients; only one patient had other associated pathologies: pulmonary tuberculosis, pleural empyema, syphilis, primary hyperparathyroidism, histiocytosis, and intestinal angiodysplasia.

TABLE IV

Clinical syndromes present

Clinical syndromes	N	%
Cardiac involvement – total	12	60
Cardiac Insufficiency	5	25
Renal involvement – total	8	40
Renal insufficiency	7	35
Kidney involvement	3	15
Non-nephr proteinuria	6	30
Peripheral polyneuropathy	6	30
Carpal tunnel syndrome	4	20
Skin manifestations (purpura, infiltrate,…)	4	20
Intestinal changes	5	25
Macroglossia	2	10
Orthostatic hypotension	3	15
Adenopathies	4	20
Hepatosplenomegaly and goiter	1 each	—
Factor X deficit	2 (of 4)	—

A two-dimensional echocardiogram was performed in 17 patients. In 13 of the patients (76%), the changes described for amyloidosis were identified, such as pericardial effusion (n=4 - 24%), valvular thickening (n=6 - 35%), thickening of the septum and ventricular walls (n=6 - 35%), diastolic dysfunction (n=6 - 35%) and the characteristic "granular speckling" appearance of the myocardium (n=3 - 17%).

Bone marrow analysis was performed in 17 of the 20 patients. It should be stressed that in eleven patients, the percentage of plasma cells was fewer than 5%, in five patients it was between 5% and 10%, and in one patient it was over 10%.

The presence of a monoclonal peak was detected by electrophoretic protein profile analysis in 5 patients. Serum immunoelectrophoresis (IEF) was carried out which detected monoclonal IgG k in four patients, IgG I in one patient, and I monoclonal light chains in three patients. The urinary IEF detected k chains in three patients, and I chains in another three patients.

The patients were classified as to the type of systemic amyloidosis, without using immunocytochemistry (which was unavailable at that date). Thus, based on clinical and laboratory criteria, nine patients without MG, pathological associations suggestive of secondary etiology, renal and hepatosplenic preferential distribution were classified as having secondary amyloidosis (AA); six other patients with MG and/or light chains in urine, distribution in the ligaments, nerves, heart and tongue, absence of pathological associations, and suggestive echocardiographic changes were classified as having primary amyloidosis (AL); the classification for the remaining five patients was unclear (AA or AL?), as they had mixed characteristics (*Table 5*)

The permanganate test was performed in eleven patients (*Table 6*). Comparing the results with the clinical classification, this test was consistent for all 6 patients with a suggested classification of AA; the results were the same for just one of the 2 patients classified as having AL; and the test diagnosed AA for 2 of the patients with an unclear classification and AL in 1. Note that the average time of diagnosis (from the onset of symptoms) was 20 months.

In December 1994, nine of the patients were still alive, five had given up the study, so their evolution is unknown, and six had died (30%). The causes of death were uremia in two patients, heart failure in two patients, gastrointestinal bleeding in one, and sepsis in another.

The mean survival after diagnosis was, in total, 20 months, ranging from 0 to 84. The mean survival was 24 months (0 to 84) for the patients who died

TABLE V

Clinical classification of systemic amyloidosis

Nonfamilial systemic amyloidosis		
AA	Without M gammopathy Suggestive pathological associations Distribution (+ hepatosplenic, renal)	N = 9
AL	M Gammopathy or light chains Distribution (+ ligaments, nerves, heart, tongue) Without suggestive associations AA Characteristic echocardiogram	N = 6
AA/ AL?	Mixed conditions	N = 5

TABLE VI

Results of the permanganate test

Clinical-lab suggestion	Permanganate test (N = 11)
AA – 6	AA – 6
	AL – 0
AL – 2	AA – 1
	AL – 1
AA/ AL? – 3	AA – 2
	AL – 1

and also for the patients who survived (1 to 42); for the patients who gave up the study, it was 8 months (1 to 14), considering the date of the last follow-up. It is noted that at 24 months, survival was 25%, and at 48 months it was only 5% (*Fig. 2*).

Discussion and conclusions

Systemic amyloidoses are rare conditions that remain underdiagnosed; in our case series, late diagnosis was observed in relation to the onset of symptoms (20 months). However, for all patients except one, the disease was diagnosed before death.

Pathological anatomy study is recommended, whether to confirm amyloidosis or for its characterization, although it should be presumed by a specific clinical context. Therefore, it is necessary that the practitioner bear in mind the most characteristic clinical syndromes, and by using non-invasive and accessible methods, increase the number of diagnoses in the earlier stages of the disease.

In our case series, we found the usual clinical manifestations observed in systemic amyloidosis, with cardiac, renal and peripheral nervous system involvement being the most common manifestations, in percentages very similar to those found in the literature (*Table 4*).

We also verified the presence of some pathological associations classically described in association with AA amyloidosis (*Table 2*): chronic pyelonephritis, pulmonary tuberculosis, syphilis, and empyema. Three patients were diabetic. In that condition, pathogenesis of AA amyloidosis can be multiple. However, we did not find, in any other case series observed, an association with primary hyperparathyroidism and intestinal angiodysplasia, which were present in two of our patients (simple association?).

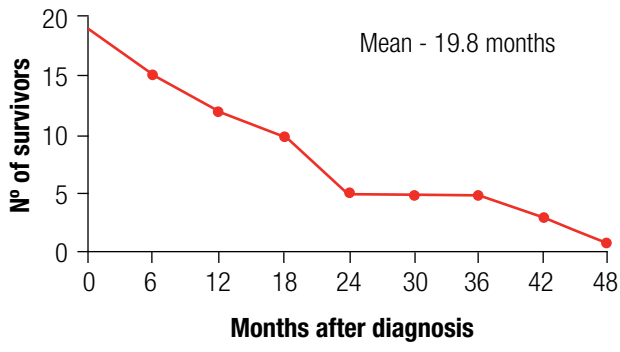
The majority of the complementary diagnostic tests that can be carried out are more useful for evaluating the patient, although some of the changes described may suggest the diagnosis, particularly in the presence of certain clinical conditions. Therefore, in this situation, the presence of anemia is not rare, the most common causes being multiple myeloma, renal insufficiency and gastrointestinal bleeding.[16] The sedimentation rate may also be elevated. It is common to find changes in renal function, and proteinuria (nephrotic or non-nephrotic) is the most frequent form of presentation of systemic amyloidosis (73%); renal insufficiency may also occur (half of the patients).[13]

Hepatic involvement is often subclinical and is indicated by elevated alkaline phosphatase. The changes are due to greater vascular fragility, and are rarely associated with impaired coagulation or lack of factor X.

It should be noted that brief urinalysis is often normal (20%) and in the absence of significant proteinuria, Bence Jones proteinuria[16] may not be noticed unless identified by electrophoresis.

Radiology may also be required, as the presence or absence of osteolytic lesions will help to distinguish between multiple myeloma and primary amyloidosis.[16] The electrocardiogram often shows low voltage or characteristics of anteroseptal infarction, even if no actual infarction has occurred (pseudoinfarction). Arrhythmias are also common.[13,17]

Three very important tests, particularly for the assessment of predictability of positivity for amyloidosis,[18] are the monoclonal component test, the bone



Nonfamilial amyloidosis - Survival.

FIG. 2

marrow test and echocardiogram.

A "monoclonal peak" in the electrophoretic protein profile occurs in about one quarter of patients (23% in our case series), approximately 50% of the patients with amyloidosis have a normal electrophoretic protein profile or one with minor changes. Hence the importance of conducting a systematic serum and urine immunoelectrophoresis in these patients.[16] About 90% of the patients have monoclonal protein in serum and/or urine.[13,16,19] Serum MG was observed in 8 patients and urinary MG in 6 patients. It should be noted that urinary immunoelectrophoresis can detect a MG even in the absence of serum monoclonal changes. It is also emphasized that, contrary to what happens in multiple myeloma, there is a predominance of chains 1 (1:k = 2:1),[16] which may be related to the physical properties of these light chains, with a greater tendency to acquire the b-pleated structure of the amyloid substance.[20]

The two-dimensional echocardiogram is still considered a non-histological diagnostic method for systemic amyloidosis. Although it is currently questioned as a more sensitive non-invasive method,[21] its performance in a patient with suspected amyloidosis is mandatory, as it may reveal early cardiac involvement (even in an asymptomatic patient), with both therapeutic and prognostic implications.[22] Echocardiographic changes were found in 76% of our patients, with a predominance of thickening of the heart walls, valves and/or septa. The standard "granular speckling" appearance of the myocardium, which is very characteristic, although non-pathognomonic of amyloidosis, was less common; it may also occur in Pompe disease, hypoplastic left ventricle syndrome, chronic renal failure, hypertrophic cardiomyopathy and left ventricular hypertrophy due to any cause.[17,23] Doppler echocardiogram for evaluation of diastolic dysfunction is useful and shows a predictive value in patients with AL amyloidosis.[13,17]

P component-labeled scintigraphy, particularly ^{123}I-labelled P component, has also been used for the diagnosis of amyloidosis.[23,24] This method, which is not available here in Portugal, has high sensitivity (85%) and specificity of 100%,[23] allowing, in addition to the identification of deposits in various tissues, their distribution, therapeutic monitoring and prognostic assessment, and it is considered one of the best investigation methods for these patients.[23,25,26,27,28] Nevertheless, because it does not allow the identification of the amyloid fibril involved, histological examination cannot be discarded. Thus, ideally, there should always be an attempt to obtain material for histological examination.[17,23,27]

In most cases, the amyloid was identified in the abdominal fat initially by puncture/aspiration. Due to technical difficulties, we obtained few positive results, therefore we used biopsy instead. Investigation in symptomatic organs was a minority, as shown in Table 3, and skin biopsy was the most frequently performed technique.

Documentation on the presence of amyloid is not enough — its classification is fundamental. Ideally, the classification should be done by immunocytochemistry, as mentioned earlier. Since this technique is not yet available here in Portugal, for the classification of patients we rely on the organs involved, the presence of MG, existence of etiological suggestion, presence of characteristic echocardiographic changes and, finally, results of the permanganate test.[18]

The classification based on clinical syndromes is somewhat debatable as, contrary to what is reported based on classical tests, there are exceptions, and overlapping syndromes may occur.[29] The presence of MG is a good indication, particularly when it is associated with a particular clinical condition. Nevertheless, it may also be a manifestation of other diseases, particularly non-Hodgkin lymphoma or multiple myeloma. The etiological suggestions, particularly if dragged over time and echocardiographic changes previously mentioned, suggest, respectively, AA and AL amyloidosis.

The potassium permanganate test, now considered low specificity, was the test we used to distinguish between AA and AL amyloidosis.

Based on these criteria and analyzing our cases, we obtained the results expressed in Tables 5 and 6. We observed that when the clinical and laboratory suggestions indicated high probability of AA amyloidosis, the permanganate test was consistent in 100% of cases. The same did not happen to a patient with AL amyloidosis. When difficulties occurred (in three cases) the test did not help the classification, and the condition remained unclear. This is not simply a methodical doubt, since it has clinical implications, particularly therapeutic and prognostic implications. ■

References

1. Robert C, Aractingi S, Prost C et al. Bullous amyloidosis – report of 3 cases

and review of the literature. Medicine 1993; 72:38-44.

2. Husby G. Nomenclature and classification of amyloid and amyloidosis. J Intern Med 1992; 232:511-512.

3. Kyle RA. Amyloidosis. J Int Med 1992; 232:507-508.

4. Kisilevsky. Proteoglycans, glycosaminoglycans, amyloid-enhancing factor, and amyloid deposition. J Int Med 1992; 232:515-516.

5. Pepys MB. Amyloid P component and the diagnosis of amyloidosis. J Int Med 1992; 232:519-521.

6. Buxbaum J. Mechanisms of disease: monoclonal immunoglobulin deposition. Hematol Oncol Clin North Am 1992; 6:323-345.

7. Vogelgesang S, Klipple GL. The many guises of amyloidosis. Postgrad Med 1994; 96:119-127.

8. Wong CK, Wang WL. Systemic amyloidosis – a report of 19 cases. Dermatology 1994; 189:47-51.

9. Gertz MA, Kyle RA. Secondary systemic amyloidosis: response and survival in 64 patients. Medicine 1991; 70:246-256.

10. Yakar S, Livneh A, Kaplan B, Pras M. The molecular basis of reactive amyloidosis. Semin Arthritis Rheum 1995; 24:255-261.

11. Lopes S, Costa A, Afonso A, Vedes J, Alexandrino B, Silva PS. Amiloidose AL ou AA – a propósito de um caso clínico. O Médico 1990; 123:165-166.

12. Hawkins PN, Pepys MB. Amyloidosis. In Malpas JS, Bergsagel DE, Kyle RA (eds.). Myeloma. Oxford: Oxford University Press. 1995:477-506.

13. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 1995; 32:45-59.

14. Kyle RA. Primary systemic amyloidosis. J Int Med 1992; 232:523-524.

15. Gabriel J, Pimenta P, Parente F et al. Amiloidose sistémica e síndrome da veia cava superior em hemodialisado crónico. O Médico 1991; 125:386-390.

16. Kyle RA, Greipp PR, O'Fallon M. Primary systemic amyloidosis: multivariate analysis for prognostic factors in 168 cases. Blood 1986; 68:220-224.

17. Gouveia D, Carranca J, Lousada N et al. Amiloidose cardíaca: revisão da literatura. Rev Port Cardiol 1996; 15(2):657-664.

18. Duston MA, Skinner M, Shirahama T, Cohen AS. Diagnosis of amyloidosis by abdominal fat aspiration. Am J Med 1987; 82:412-414.

19. Gertz MA, Kyle RA. Myopathy in primary systemic amyloidosis. J Neurol Neurosurg Psychiatry 1996; 60:655-660.

20. Glenner GG. Amyloid deposits and amyloidosis: the beta-fibrilloses. N Engl J Med 1980; 302:1283-1292, 1333-1343.

21. Cohen AS, Jones LA. Advances in amyloidosis. Curr Opin Rheumatol 1993; 5:62-76.

22. Gertz MA, Kyle RA. Amyloidosis: prognosis and treatment. Semin Arthritis Rheum 1994; 24:124-138.

23. Hawkins PN. Diagnosis and monitoring of amyloidosis. Baillieres Clin Rheumatol 1994; 8:635-659.

24. Maulin L, Hachulla E, Facon T et al. Évaluation de l'amylose primitive (AL) par scintigraphie au composant sérique amyloide P: du diagnostic au prognostic. Rev Med Interne 1993; 14:962.

25. Hachulla E, Deveaux M, Duquesnoy B, Marchandise X. Cartographie de l'amylose par scintigraphie au composant sérique amyloïde P marqué à l'iode 123: mythe ou réalité? Rev Med Interne 1994; 15:238-239.

26. Hawkins PN, Richardson S, MacSweeney JE et al. Scintigraphic quantification and serial monitoring of human visceral amyloid deposits provide evidence for turnover and regression. QJ Med 1993; 86:365-374.

27. Hachulla E, Wechsler B, Deveaux M et al. Amylose localisée ou systémique? Intérêt et limites de la scintigraphie au composant amyloïde P marqué à l'iode 123, place de la biopsie de glandes salivaires accessoires. Rev Med Interne 1994; 15:182-185.

28. Hachulla E, Deveaux M, Duquesnoy B, Marchandise X. Scintigraphie au composant amylôide P marqué à l'iode 123: une nouvelle méthode d'évaluation de l'amylose. La Presse Médicale 1994; 23:348.

29. Stone MJ. Amyloidosis: a final common pathway for protein deposition in tissues. Blood 1990; 75:531-545.