Histol Histopath (1987) 2: 413-416

Histology and Histopathology

Secondary amyloidosis and cystic fibrosis. A morphological and histochemical study of five cases

L. Bontempini[1], C. Ghimenton[1], R. Colombari[1], M. Malena[2], P. Iuzzolino[1], M. Canciani[3], C. Doglioni[1] and L. Sbabo[1]

[1]Serv. di Anatomia e Istologia Patologica, [2]Div. Malattie Infettive, [3]Regional Cystic Fibrosis Centre, Ospedale Borgo Trento, Verona, Italy

Summary. The pathological findings of five cases of amyloidosis associated with Cystic Fibrosis are reported.

Rectal biopsy led to the diagnosis of amyloidosis in four patients. In three cases the diagnosis was confirmed at autopsy, with involvement of spleen, liver, kidneys, adrenal glands, thyroid and other organs.

It seems that Secondary Amyloidosis provokes a significant, although rare, complication of Cystic Fibrosis as greater numbers of these patients survive into adulthood.

Key words: Amyloidosis - Cystic fibrosis

Introduction

Amyloidosis suggests the presence of amyloid deposits between cells in various tissues and organs of the body in a wide variety of clinical settings.

This substance is a pathological fibrillary protein, insoluble, with particular phisicochemical and ultrastructural features, responsible for its polariscopic characteristics. It originates from normal polipeptidic fragments of the serum (Skinner and Cohen, 1983).

At the present time, the Authors indicate three principal categories of systemic amyloidosis and another limited to a single organ or tissue (Skinner and Cohen, 1983; Glenner, 1980).

Secondary Amyloidosis (S.A.) is found in association with a wide variety of infectious (tuberculosis, leprosy, syphilis, osteomyelitis, pulmonary abscesses), inflamatory (rheumatoid arthritis) and other diseases, characterized by protracted breakdown of cells; on the other hand, it is rarely associated with Cystic Fibrosis (C.F.), even in patients with bronchiectasis, chronically infected (Missmahl, 1967; Ristow et al., 1977; Prior and Crawford, 1980; Vilaseca et al., 1981; Biberstein et al., 1983; Carretero Sastre et al., 1983; Travis et al., 1986).

In this paper we present five original cases of S.A. associated with C.F.

Offprint requests to: Dott. Lamberto Bontempini, Serv. di Anatomia e Istologia Patologica, Ospedale Borgo Trento, 37126 Verona, p.le. Stefani 1, Italy

Materials and methods

Out of 955 C.F. patients seen in the Regional Cystic Fibrosis Centre of Verona, we have observed five cases of S.A.: clinical features of them are reported in Table 1; in four of these patients, clinical signs of amyloidosis were confirmed by rectal biopsy, investigated with Congo-red staining and polariscopic examination (Fig. 1).

In case n°2 the gengival biopsy was negative, but clinical suspicion was confirmed by examination of autopsy specimens.

Four patients died: in three cases autopsy was performed.

The sections of rectal biopsies and of kidney and spleen have been treated as described by Wright and Coll. (Wright et al., 1977): each section was immersed in a $KMn0_4/0{,}3\%$ H_2S0_4 solution for three minutes, decolorized in 5% aqueous oxalic acid, and rinsed with distilled water.

The treated and control sections (as control-case we used a medullary carcinoma of thyroid) were stained with 1% alkaline Congo red. The specimen is said to be «sensitive» if the Congo red-stained amyloid is no longer present after potassium permanganate pre-treatment. The specimen is «resistent» if the potassium permanganate does not abolish the Congo red-stained amyloid.

Results

Clinical findings about every patient are described in Table 1.

Autopsy always showed a systemic distribution of

amyloid deposits (Table 2): we found amyloid deposits in the thyroid (Fig. 2), kidney, adrenal glands, spleen and liver of all patients; in two patients only (case 1 and 3) they were also found in the pancreas, lungs and salivary glands; lastly, we found small amyloid deposits not only in the above mentioned organs, but also in the vessel walls of lymphnodes (case 2 and 3) and heart (case 3).

With light microscope and standard tissue stain, amyloid appeared as extracellular deposits of an amorphous, eosinophilic, hyaline substance.

To differentiate amyloid from other hyaline deposits (e.g. collagen, fibrin) we used the Congo-red stain: under ordinary light, tissue deposits showed a red color; by polarizing microscope, the same deposits changed to the typical «green-apple» birifrangence.

In all specimens, staining and polariscopicéé characteristics disappeared after testing with potassium-permanganate and ossalic acid (Romhanyi, 1972; Wright et al., 1977): so we can classify these five cases without doubt as S.A.

In the control-case, amyloid deposits didn't lose staining and polariscopic characteristics after testing with potassium-permanganate and ossalic acid.

Table 1

Case n°	1 (V.E.)	2 (G.L.)	3 (P.D.)	4 (C.S.)	5 (C.F.)
sex	M	M	M	F	M
age* at diagnosis of C.F.	19	18	2	1	13
age* at diagnosis of amyloidosis	24	20	6	12	20
Clinical findings	Chronic respiratory infections, goiter, intestinal subocclusion, renal failure	Chronic respiratory infections, renal failure	Chronic respiratory infections	Chronic respiratory infections	Chronic respiratory infections, renal failure
Age at death	27	20	6	13	– (living)

*: Years

Table 2

Amyloid deposits in:	Case n°		
	1	2	3
Thyroid	+	+	+
Kidney	+	+	N.T
Adrenal glands	+	+	+
Spleen	+	+	+
Liver	+	+	+
Pancreas	+	–	+
Salivary glands	+	–	+
Respiratory system	+	–	+
Intestine	–	+	+
Others	–	vessel wall of lymphnodes	vessel wall of heart

N.T.: Not Tested

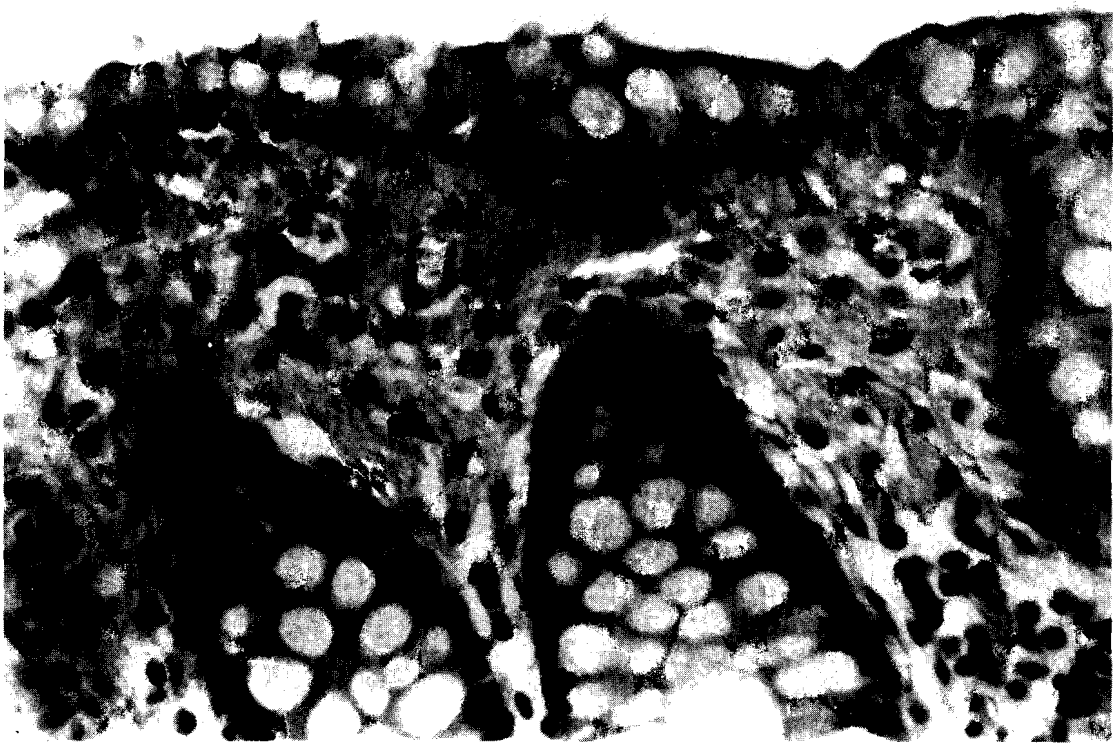

Fig. 1. Rectal mucosa: a subepithelial deposit of amyloid: arrow. Congo Red, ×400; polarized light

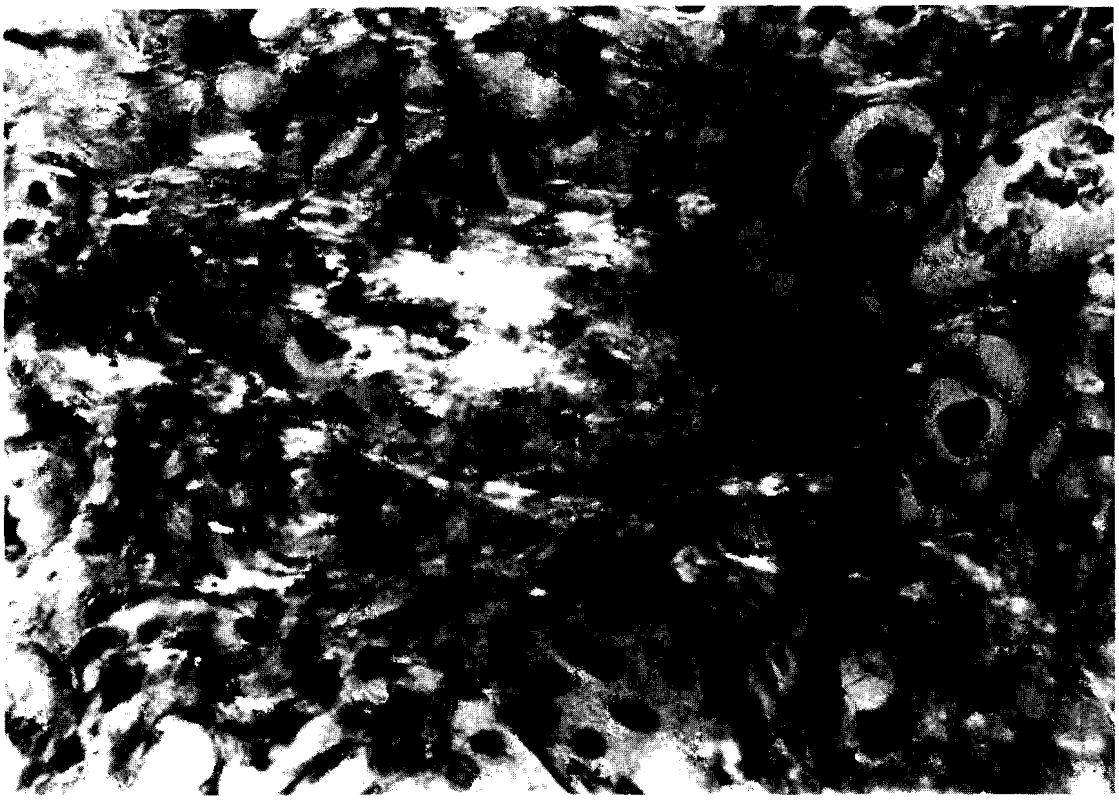

Fig. 2. Thyroid gland: a massive deposition of amyloid in the interstitium. Congo Red, ×300, polarized light

Discussion

The appearance of amyloid deposits in the patients' tissues affected by C.F. is very rarely described in Medical reports: this association has been mentioned only in 12 patients before 1985 (Travis et al., 1986).

Furthermore we can state that all our cases belong to S.A.: in fact, amyloid deposits lost staining and polariscopic characteristics after testing with potassium-permanganate and ossalic acid.

S.A. is rarely found in young patients, especially if suffering from tuberculosis and rheumatoid arthritis. Probably, chronic pulmonary infections cause the synthesis of an amyloidogenic protein (S.A.A.) and then of its fibril fragments (A.A.) in all patients affected by C.F.; but sometimes only, follow the clinical features of amyloidosis: up to this date we have not been able to find a valid explanation.

However, many Authors (Biberstein et al., 1983; Travis et al., 1986) are of the opinion that very important factors in the pathogenesis of amyloidosis are biochemical anomalies (in DNA?) in the synthesis of this S.A.A. or in the phase of digestion and/or secretion of S.A.A. and its A.A.

Another point that is still unexplained, appears when we consider the high frecuency of amyloid deposits in the thyroid of these patients affected by C.F., compared with the frecuency observed in patients suffering from S.A. not associated with C.F.: thyromegaly was observed in 3 out of 9 cases by Travis (Travis et al., 1986) and in 2 out of 5 in our experience; this symptom did not diminish after therapy with mucolitic drugs containing iodures was interrupted.

Genetic determination of this thyrofilia is probably confirmed by the fact that the same symptom has been observed in limited geographic areas (Papua, New Guinea) (Travis et al., 1986).

Finally the growing frecuency of the association of amyloidosis and C.F., in the opinion of quite all authors, is principally produced by longer life expectancy of these patients that reach adult life in greater numbers.

References

Biberstein M., Wolf P., Pettross B., Fanestil D. and Vasquez M. (1983). Amyloidosis complicating cystic fibrosis. Am. J. Clin. Pathol. 80, 752-754.

Carretero Sastre J.L., Fernández Jorge M.A., del Campo Matias F., Arenos Gutierraz J.A. and Rodrigo Parra, A. (1983). Una rara asociacion: Fibrosis quística y amiloidosis sistémica. Rev. Clin. Esp. 169, 273-275.

Glenner G. (1980). Amyloid deposits and amyloidosis. N. Engl. J. Med. 302, 1283-1292.

Missmahl H.P. (1967). Amyloidose: Klinik, therapie, prognose. Fortschr. Med. 85, 621-626.

Prior J. and Crawford A.D. (1980). Systemic amyloidosis complicating cystic fibrosis. Br. J. Dis. Chest. 74, 84-86.

Ristow S.C., Condemi J.J., Stuard I.D., Schwartz R.H. and Bryson M.F. (1977). Systemic amyloidosis in cystic fibrosis. Am. J. Dis. Child. 131, 886-888.

Romhanyi G. (1972). Differences in ultrastructural organization of amyloid as revealed by sensitivity or resistance to induced proteolysis. Virchows Arch (Pathol. Anat.) 357, 29-3.

Skinner M. and Cohen A.S. (1983). Amyloidosis: clinical, pathologic and biochemical characteristics. In: Connective tissue diseases. Wagner BM, Fleischmayer R, Kaufman N (eds). Williams-Wilkins. pp 97-119.

Travis W.D., Castile R., Vawter G., Schwachman H., Warwich W., Burke B. and Skinner M. (1986). Secondary amyloidosis in Cystic Fibrosis. Am. J. Clin. Pathol. 85, 419-424.

Vilaseca J., Cuevas J., Fresno M., Tor J., Guardia J. and Bacardi R. (1981). Systemic amyloidosis in cystic fibrosis. Am. J. Dis. Child. 135, 667.

Wright J.R., Calkins E. and Humphrey R.L. (1977). Potassium permanganate reaction in amyloidosis: A histologic method to assist in differentiating forms of this disease. Lab. Invest. 31, 274-281.

Accepted June 10, 1987