Intraorbital amyloid

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Several reviews of ocular amyloidosis have emphasized its origins in the conjunctiva and lid (Halasa, 1965; Stansbury, 1965; Smith and Zimmerman, 1966). The occurrence of orbital amyloid has been considered extremely rare, its pathogenesis speculative, and its place in the spectrum of diseases associated with amyloid deposition uncertain (Groniowski, Bernardczykowa, and Norn, 1965; Howard, 1966; Kassman and Sundmark, 1967). For this reason it is felt that further attention should be called to this entity.

Case report

A 55-year-old Negro male labourer first sought treatment at The Mount Sinai Hospital in February, 1964, because of his concern over the appearance of his left eye. He had noted the onset of protrusion of the eye 10 years earlier, without pain, visual loss, diplopia, or other ocular symptoms. There was said to have been an exposure of both eyes to lime.

The records of another hospital indicated that he had been seen 4 years after the onset and found to have a visual acuity of 20/20 in each eye, marked proptosis of the left eye with fixation of the globe, and a hard mass between the globe and the superior orbital margin. The remainder of the eye examination was recorded as being not remarkable. The general history was negative for systemic illnesses; and the physical examination was non-contributory. CBC, urine analysis, erythrocyte sedimentation rate, and albumin/globulin ratio were normal, as were radiographs of the chest, skull, paranasal sinuses, and optic foramina. The larynx and sinuses were normal on otolaryngological evaluation. A biopsy specimen of the mass was described as "having the consistency of cartilage", and showed histologically "eosinophilic strands of myxomatous material with no definite arrangement, no prominent vessels, and poor in cellular content." The diagnosis was "benign mesenchymal tumour of unknown type, most likely chondroma". Orbital exploration was performed, at which time the tumour could be seen extending to the posterior part of the orbit and into the lid structures. Only incomplete removal was possible.

The patient was seen at a second hospital in July, 1963, 9 years after the onset. Leucopenia, mild albuminuria, and a slightly elevated blood sugar level were found. Lobulated masses were palpated in the region of the previously excised mass, which on biopsy and histological examination were seen to consist almost entirely of amyloid.

At the time of his admission to Mount Sinai Hospital in 1964, examination of the left eye and orbit revealed findings similar to those already described (Figs 1 and 2, overleaf). In addition, the opposite lid contained a firm, localized, non-tender mass supero-nasally, also palpable into the right orbit. The patient was aware of its presence but was uncertain as to its date of onset. Visual acuity could be corrected to 20/20 in the right eye and 20/70 in the left. The central and peripheral visual fields were full in the right eye with a normal blind spot; the field of the left eye showed a superior constriction to 10° (possibly an artefact due to unretractable prolapsed conjunctiva, which was adherent to the upper part of the cornea), and a markedly enlarged blind spot. Intraocular pressure by applanation was 21 mm. Hg in the right eye and 13 mm. Hg in the left. Exophthalmometry readings indicated 4 mm. of proptosis of the left eye. The general physical findings were again unremarkable except for obesity; no thyromegaly, congestive heart failure, or abdominal organ enlargement were found. Albuminuria, hyperglycaemia, and mild leucopenia were present. Other renal function tests were normal, as was liver function, except for an inverted albumin/globulin ratio.

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FIG. 1 *Proptosis of left eye. Note fullness above medial canthus of right eye*

FIG. 2 *Amyloid-infiltrated conjunctiva, left eye*

Protein-bound iodine was normal. The erythrocyte sedimentation rate was significantly elevated. A trace of Bence Jones protein was detected in the urine. Electrophoresis of serum showed diffuse elevation of the gamma-globulin fraction with other components normal. Urine electrophoresis showed a preponderance of protein in the albumin position. Serum macroglobulins, cryoglobulins, and the Coombs and latex-fixation tests were negative. A Congo red test was not done because of the possible dangers associated with this procedure in the dosage appropriate for this patient's size. Radiographs of the chest, sinuses, skull, orbits, and long bones were non-contributory; an electrocardiogram indicated non-specific T-wave changes and normal rhythm with occasional atrial extrasystoles. Sternal marrow showed slight prominence of plasma cells, which appeared normal. Skin tests for tuberculosis, histoplasmosis, coccidioidomycosis, and blastomycosis were negative. Medical and haematological consultants could find no evidence of systemic amyloidosis. Neurological examination revealed absent ankle jerks and a history of occasional numbness and tingling of the extremities. Detailed sensory testing gave normal results. The patient refused rectal, gingival, renal, and liver biopsies.

On February 26, 1964, a limited exploration of the left orbit was performed (the patient at all times refused surgical intervention in the right orbit). Firm, gelatinous material was seen diffusely infiltrating the orbit and upper lid (Fig. 3). Removal of the mass was not possible. A large biopsy was taken, which again proved to be amyloid (Fig. 4), as did a conjunctival biopsy (Fig. 5). Immunofluorescence studies on the specimen indicated 7S gamma globulin in bloodvessel walls. A portion of the specimen was cultured and was negative for fungi and acid-fast bacilli. Post-operatively there was no improvement. The patient has become lost to follow-up, and further search for an underlying systemic disease has not been possible.

Discussion

Amyloidosis is a condition characterized by extracellular deposition in tissues of a substance with certain special staining characteristics. It was once considered a degenerative process involving the deposition of carbohydrates, but is now felt to be a disturbance of protein synthesis, more specifically an infiltration of glycoproteins of variable composition, produced by plasmacytic cells of the reticuloendothelial system (Teilum, 1957). By histochemical techniques it has been shown that there are structural and antigenic similarities between amyloid and gamma globulin, and between amyloid and Bence Jones protein and other myeloma proteins (Vazquez and Dixon, 1956; Osserman, 1959a; Magnus-Levy, 1952), particularly the 7S and 19S fractions. However, in experimental amyloid deposition following prolonged antigenic stimulation, the abnormal substance remains in the involved area instead of entering the general circulation, suggesting a difference from normal gamma immunoglobulins (Osserman, 1961).

FIG. 3 Surgical exposure of amyloid mass, left orbit

FIG. 5 Conjunctival biopsy, left eye. Extensive amyloid deposition. Haematoxylin and eosin. $\times 40$

FIG. 4 Plasma cell accumulation in vessel walls and in surrounding amyloid-infiltrated orbital tissues. Haematoxylin and eosin. $\times 384$

It has been customary to classify amyloidosis into primary and secondary forms, although this is often difficult because of incomplete understanding of the cause and abnormal chemistry of this condition. One classification is given in the Table (overleaf).

Grossly, amyloid-infiltrated tissue is firm, pale, and waxy. Histologically, amyloid is an amorphous eosinophilic substance with characteristic, although at times non-uniform, staining reactions. It most notably involves small arteries and is also found as nodular deposits in mesenchymal tissues. In a single case there is very little uniformity of involvement.

The diagnosis of amyloidosis is generally considered to be most reliably made by biopsy of suspected organs (tongue, rectum, liver, kidney, bone marrow, and peripheral nerve). The Congo red test is much less reliable and not without danger. Plasmacytosis of the bone marrow is a frequent finding, in both primary and secondary forms. The plasma cells are normal in appearance and need not indicate an underlying myelomatosis (Conn and Sundberg, 1961).

Ocular involvement may be found in both primary and secondary amyloidosis. Conjunctival infiltration is usually a feature of the localized form, either associated with previous trachoma (Mathur and Mathur, 1959) or as a plasmacytoma. The localized ocular form affects young adults, is bilateral in two-thirds of cases, and usually involves both the bulbar and palpebral conjunctivae to a massive extent, with late involvement of the tarsus.

Table *Classification of amyloidosis*

I. Primary No preceding disease; involves mesodermal tissue. Mainly involves heart, gastrointestinal tract, lymph nodes, and smooth and striated muscle	
A.	Generalized
B.	Familial: peripheral neuropathy
C.	Respiratory
	(1) Tumorous: Single or multiple nodules
	(2) Diffuse
II. Secondary With predisposing disease, usually a chronic infection; also Hodgkin's disease, rheumatoid arthritis. Involves spleen, liver, kidneys, adrenals. Kidneys may also be involved in primary form	
III. Senile cardiac	
IV. Associated with multiple myeloma	
V. Localized amyloid tumours Bladder, pharynx, larynx, urethra, eye	

Ptosis due to tarsal and/or levator muscle infiltration has been reported (Guerry and Weisinger, 1960; Richlin and Kuwabara, 1962). Corneal (McPherson, Kiffney, and Freed, 1966) and vitreous opacities have been described. The vitreous deposits are considered specific in appearance and may precede by many years any clinical evidence of generalized amyloidosis (Kaufman and Thomas, 1959). Retinal periarteritis has been noted (Falls, Jackson, Carey, Rukavina, and Block, 1955).

Many investigators believe that some cases of "primary" amyloidosis are actually instances of occult myeloma or, more generally, of plasma cell dyscrasia, without other clinical evidence. The tissue infiltrates can precede by years the overt manifestations of myeloma. This is especially true in cases that show either Bence Jones proteinuria or hyperglobulinaemia, as did this patient. This observation relates more to generalized amyloidosis than to its localized or familial forms (Osserman, 1959a; Osserman, 1961; Kyle and Bayrd, 1961). The immunochemical relationship of these substances to amyloid and myeloma globulin has already been mentioned. Osserman noted that there was a group of myeloma patients with initially normal skeletal radiographs, who showed proteinuria without renal insufficiency and with evidence of abnormal infiltrates in various tissues (Osserman, 1959b). Cohen (1967) reviewed current thinking concerning the experimental and clinical aspects of amyloidosis.

It is recognized that generalized amyloidosis has not been excluded in this patient; however, regardless of the presence or absence of associated disease, involvement of the orbit by amyloid is an extremely unusual condition. Coats (1915) described a case in which increasing proptosis, reduction of vision, induration and nodular hypertrophy of the conjunctiva, and loss of all motility occurred over a 16-year period. Optic atrophy was noted, but amyloid change was found only in the ciliary muscle, the episclera, and the dural sheath of the optic nerve.

Picó (1961) reported two cases of amyloidosis of the conjunctiva, in which hypothyroidism appeared 6 to 8 years after the first evidence of ocular amyloid. Picó suggested that the primary conjunctival changes might have been myxoedematous infiltration, preliminary to the development of amyloid through changes in chemical composition.

In the present patient, there was no evidence of hypothyroidism during a 10-year interval from the onset of the orbital disease.

Mishra (1962) called attention to the possible role of trauma in the aetiology of localized amyloid change.

The most unusual feature of the present case is that the conjunctiva, although extensively involved in the left eye, apparently became so after the orbital involvement, as evidenced by the fact that the initial manifestation was proptosis; this is in contrast to the usual sequence of events in ocular amyloidosis, suggesting a primary orbital origin. Moreover, the contralateral orbit is now showing a mass with as yet no grossly visible evidence of conjunctival infiltration; biopsy of this tissue has not been allowed by the patient.

Summary

A 55-year-old Negro male had a 10-year history of progressive proptosis of the left eye, with immobility, conjunctival hypertrophy, and decreased vision. Study of the involved tissues, after an initial diagnosis of chondroma, revealed the presence of amyloid. The mass recurred and reached its former size despite an almost total removal; this has been noted in other case reports. Examination of the contralateral orbit has suggested the presence there of a similar involvement. A detailed systemic investigation was undertaken, although biopsies of other organs could not be obtained. A classification of amyloidosis is given, and the apparent rarity of orbital amyloidosis is noted.

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