PRIMARY SYSTEMIC AMYLOIDOSIS PRESENTED AS A DIAGNOSTIC PROBLEM IN ONE CASE

By C. H. Tay, A.M., M.B., B.S., M.R.C.P.(G)

(Senior Medical Registrar, Medical Unit II, General Hospital, Singapore, 3)

INTRODUCTION

Systemic amyloidosis is a rare disease, but it is now assuming an increasingly important role in the western countries as evidenced by sizeable recent reports (Dahlin, 1949; Mathews, 1954; Rukavina *et al*, 1956; Symmers, 1956; Kimball, 1961; Blum *et al*, 1962; Briggs, 1961; Brody *et al*, 1964; Casad *et al*, 1965; Brandt *et al*, 1968). In this country, however, systemic amyloidosis is exceedingly uncommon, but the primary cutaneous form known as Lichen amyloidosis is frequently seen (Tay and DaCosta, 1970; Leong *et al*, 1969). Genetic as well as racial factors have been implicated in the latter condition (Sagher *et al*, 1963; Porto *et al*, 1963).

Classically, systemic amyloidosis has been divided into three groups, according to association with other diseases and distribution in various organs. *(1)* Primary systemic amyloidosis—where there are no known associated diseases. Familial history may be obtained (Rukavina *et al*, 1956; Butterworth *et al*, 1962). *(2)* Systemic amyloidosis secondary to multiple myeloma and *(3)* Systemic amyloidosis due to various diseases such as those with chronic suppuration and prolonged immunological stimulations. The first two conditions involve mainly the mesenchymal tissues, whereas the last group commonly affects the parenchymatous organs.

In most studies, the major apparent features of Systemic amyloidosis were renal (60 to 80%), cardiac (50 to 90%), gastrointestinal (30%) and other systemic lesions. Cutaneous and mucosal lesions were rare (20 to 40%) (Goltz, 1956; Cairns, 1968; Brandt *et al*, 1968). Often associated with a haemorrhagic tendency, skin lesions are discrete papules or nodules found on any part of the body, but the majority are distributed around the eyes, nose, mouth, trunk and extremities. Atypical forms like subcutaneous nodules, confluent plaques, and scleroderma-like lesions have been described (Binley, 1938; Miescher, 1945; Butterworth *et al*, 1962).

In this paper, a patient with extensive spontaneous and induced haemorrhagic tendency and gross skin lesions with atypical features is described. Due to the unfamiliarity of this condition, the case posed a diagnostic problem in various specialist units for over 3 years before the diagnosis was established.

CASE REPORT

In 1965, a 74-year-old Chinese ex-seaman first noticed a cluster of non-itchy yellowish papules on the upper eyelids without any other symptoms. He was in excellent health and there were no other systemic or skin disorders. There was a past history of having contacted veneral disease about 25 years ago, and he was treated with courses of injections. By mid-1966, skin lesions had grown gradually in size and spread around the periorbital region. He consulted a number of medical practitioners for the unsightly appearance of the face, but none could offer any diagnosis or effective treatment. A few months later, some of the periorbital papules became nodular in size and some coalesced to form plaques. Easy bruising of the skin, especially over the lesions on the eyelids, was then observed. Cutaneous bleeding became a troublesome problem, as slight pressure applied over the skin of the eyelids could instantaneously produce a large haematoma. Superficial bruises tended to ulcerate and produce chronic septic ulcers of the skin. He was referred to the Eye Department of the General Hospital because the periorbital lesions had grown to such an extent that the vision of both eyes was obstructed. Attempts to elevate the upper lids caused periorbital haematoma, and septic conjunctivitis and blephritis were produced by obstruction and stasis of the ocular secretions. Although ocular sepsis was checked by antibiotics, the ophthalmologists could not find any common causes of periorbital bleeding nor could they establish the nature of the eye lesions. The 'Leonine' facial appearance prompted the eye-specialists to refer him to the Skin Hospital for the exclusion of Leprosy. Extensive investigation in this hospital did not confirm the suspicion of Hansen's disease. Nor did they find any evidence of tuberculosis, sarcoidosis, xanthomatosis, lipoid proteinosis, or syphilis. History of exposure to drugs or

chemicals was not obtained. Haematological and biochemical tests were within normal limits. Bleeding time, clotting time, and Hess's tests were also normal. For lack of diagnosis, he was labelled as "allergic" dermatitis and blephritis and was treated symptomatically with antihistamines and hydrocortisone and antibiotic eye-drops.

In January 1968, an E.N.T. specialist's opinion was sought because the papulonodular lesions had involved the nose. The larger polypoid masses in the nostrils had blocked the nasal passage. The possibility of the masses being some malignant growth arising from the nasopharynx could not be excluded, because of the contact bleeding and infiltrative nature of the nodular masses. Ulceration was not a dominant feature. Examination of the oro-nasopharynx failed to detect any growth from these areas. Polypoid lesions were found to be originated from the skin, which was indurated, smooth and shining. A postnasal biopsy revealed no neoplasia. It was then noted that this patient might be suffering from some systemic diseases, as the haemorrhagic tendency was by then more prominent and extensive. Purpura and ecchymosis were found on the chest, both arms and the mouth. He was referred to the Medical Unit with a provisional diagnosis of ? Scurvy, ? Reticulosis or ? Leukaemia.

Further history, on his admission to the medical ward, did not shed much light on the aetiology of his disease. He was not known to be sensitive to any drugs, food or known substances. He had no fever, weight loss, chronic sepsis, bone pain, swelling of legs or face, palpitation or chest pain. Apart from cutaneous bleedings, there was no history of haematemesis, melaena, haemoptysis or haematuria. Detailed dietary history including intake of fruits was found to be adequate, although he had not been eating normally two weeks prior to the admission because of the soreness of tongue and bleeding from mouth ulcers. He did not take alcoholic drinks and also refrained from tobacco smoking. Family history did not reveal any systemic or skin diseases. The patient lived in retirement and was being looked after by his wife, children and grandchildren.

On physical examination, his general condition was good and there was no pyrexia, anaemia, clubbing or oedema. Dyspnoea and cyanosis were not present. Lymph nodes were not enlarged. Purpura and ecchymosis were found on the face, chest, outer surfaces of arms and legs and the trunk (Figs. 1 and 2). On his face, areas of bleeding and small haematomata were seen on the forehead, around the eyes, nose and mouth, and on both cheeks and the chin. Massive plaque-like infiltrations and some papulonodular lesions surrounded the periorbital areas causing swelling and thickening of the skin. Both eyes were covered up by the thickened plaques of the eyelids. Large polypoid masses, measuring one to $\frac{1}{4}$ inch were found around the nostrils. Also present were numerous papules and nodules of various shapes and size in this area. Both lips, especially the upper lip, were markedly enlarged and swollen. The cutaneous lesions were all smooth, shining, and firm and not tender. The colours vared from transparent, opalescent simulating vesicles, to waxy, bluish and frank haemorrhagici. Hypoaesthesia was not elicited. Firm pressure over the affected skin, like lifting the eyelids, would readily detach the superficial skin and result either in the formation of haemorrhagic blisters or frank bleeding. Icterus of both sclera was observed, presumbly from excessive haemolysis. Petechial haemorrhages were present on the buccal mucosa, palate, tongue and tonsils. Slight enlargement of the tongue was noted. The fingers were swollen and rigid, and the skin was smooth and hide-bound. Raynaud's phenomena was not observed, and there were no joint deformities. The pulse was 100 per minute, and the heart was clinically normal, although cardiomegaly was present on X-ray Chest and there were electrocardiographic abnormalities. The lungs were clear. The liver was 2 fingers—breadth enlarged below the costal margins. The spleen and kidneys were not felt. The central nervous system was essentially normal. There was some thickening of the peripheral nerves—the ulnar and peroneal nerves were palpalated, but there were no sensory changes. Rectal examination was normal.

INVESTIGATIONS

Hb. 11 Gm.%, W.B.C. 11,000/c. mm. Polymorph 89%, Lymphocyte 6%, Monocytes 2%, Eosinophils 3%; Platelet count 220,000/c. mm.; Reticulocyte Count 1%; Bleeding time 3 min.; Clotting time $2\frac{1}{2}$ min.; Prothrombin time 3 min.; Hess's Test—negative. E.S.R. 84 mm./hr.

Urine examination—no red or white cells or casts. Traces of albumin present only. Urine negative for bile but positive for urobilinogen. Blood urea—43 mg.%; Blood Kahn test—negative; Serum bilirubin 0.3 mg.%, Serum alkaline phosphatase 7.6 units; Serum glutamic pyruvic transmainase—82 King Armstrong Units. Serum protein electrophoresis—Albumin 3.2 Gm.%,

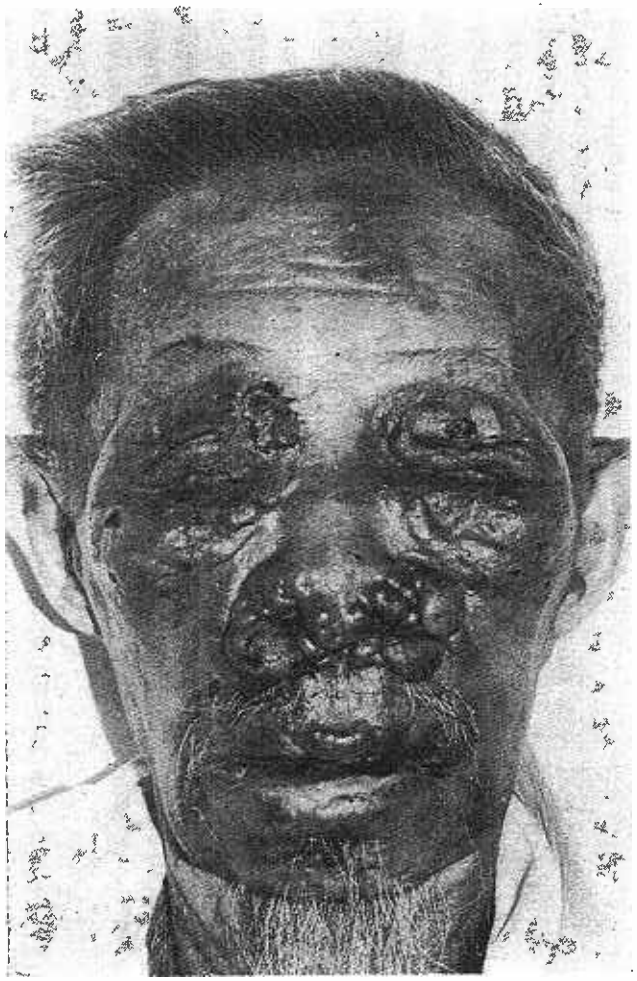

Fig. 1. The 'Leonine' facies produced by extensive plaques and papulonodular masses around the eyes and nose. Both lips were thickened and swollen. Note the cutaneous haemorrhages on the forehead, over the lesions of the eyes, cheek, nose and mouth.

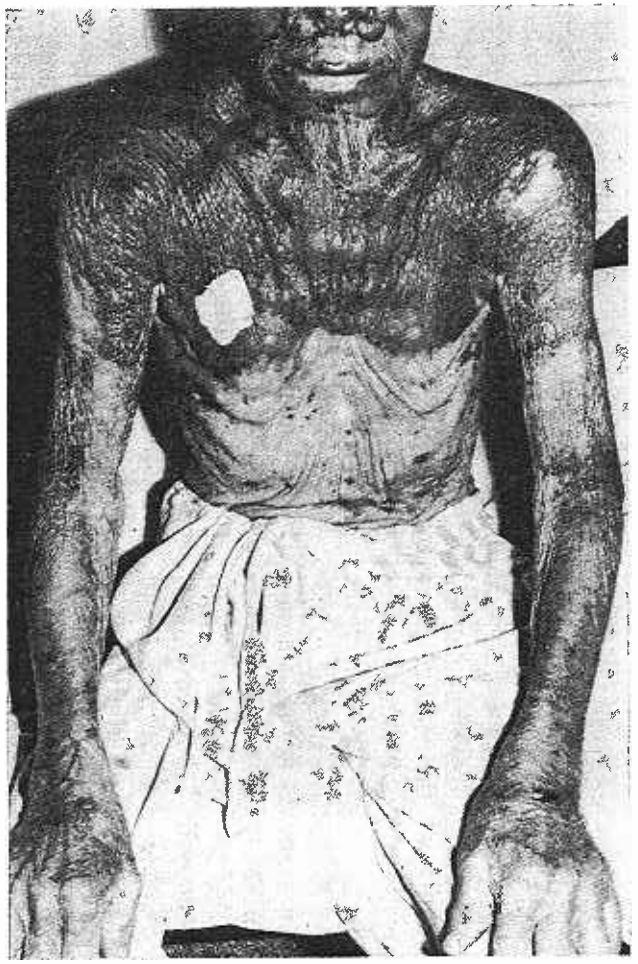

Fig. 2. Widespread skin purpura, ecchymosis and petechie on the trunk and upper limbs. Note the scleroderma-like lesions of the fingers.

alpha-1 0.2 Gm.%, alpha-2 0.6 Gm%, beta. 0.4 Gm.%, Gamma 4.1 Gm.%, Total serum proteins—8.5 Gm.%. Rheumatoid factor and L.E. cells were negative. X-ray chest revealed moderated enlargement of the heart. Lung fields were clear. Skull X-ray was normal, and mild osteoporosis was found in the X-ray of lumber and thoracic spines. E.C.G. showed generalised low voltage Q.R.S. complexes with flattened or inverted 'T' waves in all chest leads.

SPECIAL TESTS

Whole blood clotting time—8 min. (Normal less than 10 min.).

Partial Thromboplastin Time—78 sec. (Normal less than 100 sec.).

Prothrobin Time (Quick)—15 sec. (Normal 15 sec.).

Platelet aggregration test, Fibrin stabilising factor and thromboplastin generation tests were all normal. Bone marrow was also normal. Blood Vitamin C estimation—30 microgram per 100 Gm. W.B.C. (Normal 25 to 38 mcg.).

Urine for Bence Jones protein—negative × 3; Blood for cold agglutitin—negative; Immunoelectrophoresis did not reveal abnormal immunologlobulins, but IgG. was slightly raised.

I.V.P. was normal; Intravenous Congo-red test—73% dye present after one hour. Ear clip for acid-fast bacilli (×3)—negative.

A biopsy of the nasal polyp was carried out by the E.N.T. surgeon for suspected naso-pharyngeal carcinoma or lymphoedema from obstructed lymphatics from other growths. It was reported as consistent with simple fibroepithelial polyp (using routine stains).

PROGRESS

The only positive findings in the investigations were a raised erythrocyte sedimentation rate and hypergammaglobulinaemia. The haematologist could not determine the cause of bleeding tendencies, and the ophthalmologist failed to understand the eye lesions although the patient was treated symptomatically as "? allergic blepheritis". He was discharged after the 3rd week without a diagnosis.

One month later, he was readmitted for widespread cutaneous haemorrhages of a spontaneous nature, and worsening of the skin lesions on the face. The tongue was swollen, turgid and haemorrhagic and petechial haemorrhages were also found in the hard and soft palate and buccal mucosa. Iron deficiency anaemia due to chronic skin bleeding was present. The other signs were essentially the same as before.

At this stage, primary systemic amyloidosis was suspected although he had a normal Congo-red test. Biopsy of one of the nodules around the nose was taken and special stains for amyloid were requested. The histology report was as follows: "Section showed extensive amyloid deposits in the dermis completely replacing normal tissue" (Fig. 3).

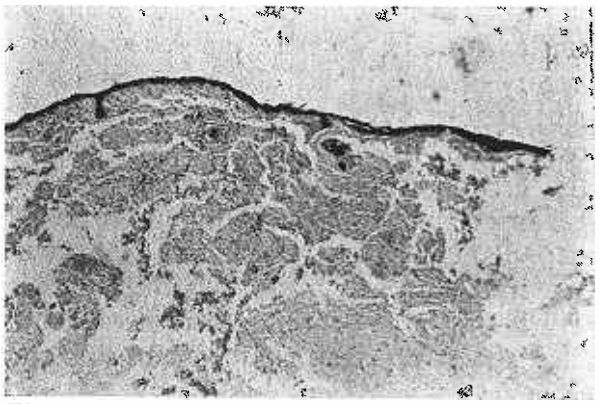

Fig. 3. Skin biopsy of papule on the face (low magnification). Showing extensive masses of homogenous eosinophilic material in the dermis completely replacing the normal tissue. Stained with Congo-red.

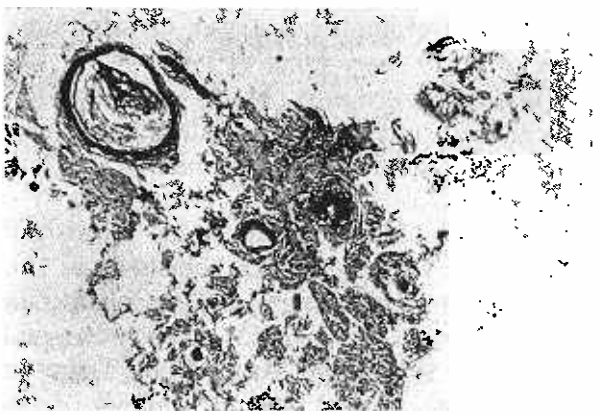

Fig. 4. Rectal biopsy (low magnification). Showing amyloid material around blood vessels and connective tissue stroma. Stained positive with Congo-red, methyl violet, crystal violet and fluoresced with Thioflavin-T under polarised microscope.

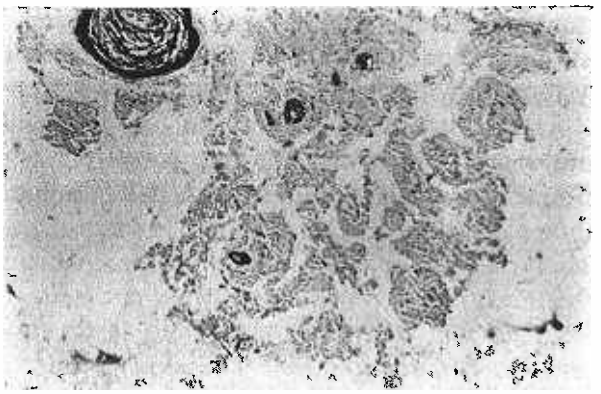

Fig. 5. Tongue biopsy (low magnification). Same as Fig. 4.

Tongue and rectal biopsies were also done and both sections showed masses of homogeneous eosinophilic material around vessels and in connective tissue stroma. This material was Congo-red positive, methyl violet-positive and fluoresced with ultraviolet light after staining with Thioflavin-T stain under a polarising microscope (Figs. 4 and 5).

He refused biopsy of liver and kidneys and had himself discharged against medical advice.

On April 1969, he was brought into hospital for suspected drug allergy because of his skin bruises. Again he was misdiagnosed as a case of Leprosy because of his grotesque features and facial lesions. The nature of the illness was obvious after the old case notes were traced. His general condition remained good and unchanged but the cutaneous lesions had deteriorated. Papulonodules on the face had become more numerous and bigger but there were no fresh lesions elsewhere. Further investigations failed to detect multiple myeloma or other secondary causes of amyloidosis.

DISCUSSION

Recent studies have shown numerous instances of overlapping in tissue distribution of amyloid in the three types of systemic amyloidosis—the primary amyloidosis, the myeloma-associated form, and the secondary form due to other diseases. It has also been proven that amyloid material of all sources, either primary or secondary, systemic or localised, is basically similar by immunological, biochemical and ultrastructural investigations (Cohen and Cakins, 1959; Cohen, 1965; Hashimoto *et al*, 1965; Gafni *et al*, 1966; Azar, 1966). There was no difference in the clinical features, course and prognosis in these 3 groups studied by Brandt *et al* (1968).

The diagnosis of this patient was established by positive skin, tongue and rectal biopsies for amyloidosis after a long process of exclusion of common conditions. Additional evidence of systemic involvements were macroglossia, hepatomegaly, minimal albuminuria, cardiomegaly and electrocardiogram changes consistent with diffuse myocardial damage, thickened peripheral nerves and the gross skin lesions. It was assumed that he had the Primary form since there were no secondary causes such as multiple myeloma or other associated diseases, and family history was negative for amyloidosis. The skin lesions, although atypical and severe, were commonly seen in the primary systemic type. Haemorrhagic tendency present in our case is one of the hallmarks of this disorder. Often the cutaneous bleeding arises spontaneously or upon slight trauma or friction (Eisen, 1946; Thingstad, 1951; Butterworth *et al*, 1962).

The long delay in the diagnosis was partly due to the general unawareness of this condition and partly due to the failure of various specialised units to integrate all the signs and symptoms of this case into a single disease entity. Hence, while different localised lesions were separately investigated, the systemic nature of the patient's illness was not realised until much later. Thus he was suspected of suffering from local ocular diseases when he first reported to the ophthalmologist with the early skin lesions. The papular lesions resemble xanthelasma or xanthoma, colliod milium, papular mucinosis, scleromyxoedema, lipoid proteinosis, cystic lesions or allergic dermatitis with conjunctivitis. Granulomatous lesions such as sarcoidosis, tuberculosis and leprosy were also suspected. When periorbital bleeding was severe, causing bilateral periorbital haematoma, extrinsic ocular, intraocular and intracranial lesions were looked for, but no obvious pathology was found. Secondary ocular sepsis and intracable blephritis developed as a result of obstruction and bleeding from hypertrophic lesions around the eyes. The chronicity of this ocular disorder as well as its progressive nature could in most instances exclude conditions like acute infection, allergic manifestation, trauma and malignancies. The history was in favour of an infiltrative disease.

The high incidence of nasopharyngeal carcinoma among elderly Singapore Chinese prompted the attending physician to refer him to the E.N.T. department because of the polypoid masses in and around the nostrils. Malignancy was thought to be a possibility since there was nasal bleeding from contact. Complete oronasopharyngeal examination including a blind postnasal biopsy failed to demonstrate any neoplasia. There were no haemangioma, telangiectasia, granulomata, or trauma, as the tumours originated from the skin. Cutaneous metastasis from nasopharyngeal cancer has seldom been seen in this region. Moreover, such patients seldom survived for over 3 years without any therapy.

Cutaneous lesions of Primary systemic amyloidosis are characteristically non-itchy, smooth, firm, transparent or waxy papules or nodules found predominently around the orifices of the face. Lesions are often indistinguishable from other infiltrative diseases like xanthomatosis

(Cholesterol deposits), papular mucinous, lichen myxoedematosus, scleromyxoedema (mucin deposits) and colloid millium (colloid deposits). These conditions can be differentiated from amyloidosis by special stains. Colloid milium greatly resembles amyloid in sections with haematoxylin and eosin and stains positive with Thioflavin-T. However, the former condition does not stain with Congo-red or methyl violet.

The 'Leonine' facies produced by massive plaques in this patient misled the clinicians to a diagnosis of Lepromatous leprosy since such presentations are not uncommon in the advanced cases of Hansen's disease. Suspicion of this malady was strengthened by the findings of thickened peripheral nerves. Absence of sensory changes and the presence of a dominant haemorrhagic disorder served to exclude this disease. Leprosy was not confirmed by ear clips for acid-fast bacilli and the skin biopsy was negative for this disease. The bleeding disorder presenting widespread purpura and ecchymosis of the skin and the mucous membranes was extensively investigated in the medical ward. Common medical conditions were looked for and excluded. Ascorbic acid deficiency, thrombocytopenia, syphilis, haemorrhagic telangiectasia, haemophilia and other clotting and bleeding disorders, metabolic diseases, allergic disorders and collagenosis were not found. Occult malignancies like reticulosis, leukaemia, and plasma cell dyscarsias and visceral tumours were absent in this case. The only positive finding was a high erythrocyte sedimentation rate and hypergammaglobulinaemia, and these led one to investigate the possibility of multiple myelomatosis, macroglobulinaemia, cryoglobulinaemia, and other autoimmune disorders. Repeated tests failed to yield any positive results. Even the intravenous Congo-red test was not at all helpful in this case.

In contrast with primary systemic amyloidosis, Lichen amyloidosis, a primary localised cutaneous disorder is never found on the face, except for one single report (Wooldridge, 1960). In the latter condition the predominent lesions are small discrete yellowish papules of long standing, extremely pruritic and distributed on the shins and thighs. Systemic involvement is never present and haemorrhages have not been described. In fact, a diagnostic point in favour of systemic amyloidosis is the cutaneous haemorrhages induced by firm pressure over the lesion (Hurley and Weinberg, 1964). The bleeding is due to extensive amyloid deposits within and around the superficial blood vessels. In severe cases, the media and adventitia of the small arteries and veins of the whole body may be entirely replaced by amyloid. Deposits may be found in all the internal organs, the musculature as well as the skin. Typically, amyloid stained red with Congo-red, metachromatically with touldine blue, methyl violet, crystal violet, and fluoresced with Thioflavin-T stain under polarised microscope, and ultraviolet light.

Since there were no known secondary diseases in this patient, treatment was entirely symptomatic. His prognosis is considered fairly good because of the minimal internal involvement. He has survived over 3 years and his general health is still good. In Brandt's (1968) series, the mean survival time after diagnosis was eleven months. The major cause of death was renal complications (43%), but a significant 29% had sudden death of unexplained causes.

SUMMARY

A case of Primary systemic amyloidosis presenting with extensive haemorrhagic tendency of unknown origin and gross atypical cutaneous lesions on the face is described. This patient was a problem of diagnosis for over three years partly because of the general unawareness of this disease and partly because of the unusual presentations. The differential diagnosis and difficulties in the diagnosis are discussed.

ACKNOWLEDGEMENT

I wish to thank Prof. O. T. Khoo, head of Medical Unit II, for his permission to publish this case.

REFERENCES

1. Azar, H. A. (1966): "Amyloidosis and Plasma cell disorders." Ann. Rev. Med., 17, 49.
2. Bero, G. L. (1957): "Amyloidosis—Its clinical and pathologic manifestations, with a report of 12 cases." Ann. Int. Med., 46, 931.
3. Binley, G. W. (1938): "Primary systemic amyloidosis." Arch. Derm. Syph., 37, 330.
4. Blum, A. and Sohar, E. (1962): "The diagnosis of amyloidosis." Lancet, 1, 721.
5. Brandt, K., Cathcart, E. S., Cohen, A. S. (1968): "A clinical analysis of the course and prognosis of 42 patients with amyloidosis." Amer. J. Med., 44, 955.
6. Briggs, G. W. (1961): "Amyloidosis." Ann. Int. Med., 55, 943.
7. Brody, I. A., Wertlake, P. T., Laster, L. (1964): "Causes of intestinal symptoms in Primary systemic amyloidosis." Arch. Intern. Med., 113, 512.
8. Butterworth, T. and Strean, L. P. (1962): "Clinical Genodermatology." Williams and Wilkins Co., Baltimore, p. 170.

9. Cairns, R. J. (1968): "Text book of dermatology." 1st Ed. Vol. 2. Edited by Rook, A., Wilkinson, D. S., Ebling, F. J. D., Blackwell Sci. Pub. Oxford and Edinburgh, p. 1623.
10. Casad, D. E., Bocian, J. J. (1965): "Primary systemic amyloidosis simulating idiopathic ulcerative colitis." Amer. J. Digest. Dis., 10, 63.
11. Cohen, A. S. (1965): "Medical progress. Amyloidosis." New Eng. J. Med., 227, 524; 574, 628.
12. Cohen, A. S., Cakins, E. (1959): "Electron microscopic observations on a fibrous component in amyloid of diverse origins." Nature, 183, 1202.
13. Dahlin, D. C. (1949): "Amyloidosis." Proc. Staff. Meeting. Mayo Clinic, 24, 637.
14. Eisen, H. N. (1946): "Primary amyloidosis." Amer. J. Med., 1, 144.
15. Gafni, J., Merker, H. J., Shibolet, S., Heller, H. (1966): "On the origin of amyloid." Ann. Int. Med., 65, 1031.
16. Goltz, R. W. (1956): "Systematised amyloidosis—a review of skin and mucous membrane lesions and a report of 2 cases." Medicine, 31, 239.
17. Hashimoto, K., Gross, B. G., Lever, W. F. (1965): "Lichen amyloidosis—Chemical and electron microscopic studies." J. Invest. Derm., 45, 204.
18. Hurley, H., Weinberg, R. (1964): "Induced intralesional haemorrhage in Primary systemic amyloidosis." 89, 678.
19. Kimball, K. G. (1961): "Amyloidosis in association with neoplastic diseases. Ann. Int. Med., 55, 958.
20. Leong, Y. O., Tay, C. H., Foo, J., DaCosta, J. L., Tan, K.K. (1969): "Lichen Amyloidosis in Singapore." A clinical study of 142 cases. Paper read at the second World Congress of the International Society of Tropical Dermatology. Kyoto, Japan. August 15-18, 1969.
21. Mathews, W. H. (1954): "Primary systemic amyloidosis." Amer. J. Med. Sc., 228, 317.
22. Miescher, G. (1945): "Beitrag zur klinik der Paramyloidiose." Dermatologica, 91, 177.
23. Porto, J. A., Humberto, T. C., Ismelia, A. A. (1963): "Localised cutaneous amyloidosis—presence of an atypical serum globulin." J. Invest. Derm., 40, 169.
24. Rukavina, J. G., Block, W. D., Jackson, C. E., Falls, H. F., Carey, J. H., Curtis, A. C. (1956): "Primary systemic amyloidosis—a review and an experimental genetic and clinical study of 29 cases with particular emphasis on the familial form." Medicine, 35, 239.
25. Sagher, F., Shanon, J. (1963): "Amyloid cutis—Familial occurrence in 3 generations." Arch. Derm., 87, 171.
26. Symmer, W. St. C. (1956): "Primary Amyloidosis—A review." J. Clin. Path., 9, 187.
27. Tay, C. H., DaCosta, J. L. (1970): "Lichen amyloidosis." Brit. J. Derm., 82,129.
28. Thingstad, R. (1951): "Primary Amyloidosis." Acta. Med. Scand., 140, 1.
29. Wooldridge, W. E., Frierichs, J. B. (1960): "Amyloidosis—A new clinical type." Arch. Derm., 82, 230.