Atypical Amyloidosis Associated With Nonthrombocytopenic Purpura and Plasmocytic Hyperplasia of the Bone Marrow

By Simon Propp, M.D., William B. Scharfman, M.D., Richard T. Beebe, M.D., and Arthur W. Wright, M.D.

This report is concerned with two patients whose clinical and laboratory findings were strikingly similar and unusual. Both were admitted to the hospital because of unexplained skin purpura of peculiar localization about the eyes, breasts, and thighs, which had been present for two to three years. No significant hematologic abnormality was discovered until marrow aspirations revealed a marked increase in plasma cells.

A skin biopsy from the first patient was thought to contain a diffuse myxedematous deposit whereas in the second patient a similar deposition of hyalin was recognized as amyloid or an amyloid-like material. Macroglossia developed in each patient and became massive in one. Before death a large amount of thick, gelatinous material was obtained by sternal marrow aspiration from each patient. This was found to be a hyaline substance which was subsequently considered to be amyloid or an amyloid-like substance. Smears of this material contained focal collections of plasma cells.

These two patients with nonthrombocytopenic purpura of similar distribution and long duration, showed abnormal plasma cell hyperplasia and apparent gross amyloid in the marrow aspirate. They did not, however, exhibit other findings consistent with multiple myeloma or plasma cell leukemia and apparently died from amyloidosis. Postmortem examinations revealed generalized atypical amyloidosis which had the characteristic distribution of the primary type. There was no evidence of myeloma.

Case Reports

Case 1

M. T., a white woman, aged 57, was admitted to the Albany Hospital on August 2, 1949. For three years prior to admission she had suffered from a hemorrhagic rash about the eyes, in the axillae, about the breasts, and in the mouth. These lesions had gradually grown worse and had become very extensive. She had also noticed progressive enlargement of her tongue for two years. Shortly before hospitalization she suffered from shortness of breath and swelling of the ankles. Although she had been under medical care since the onset of her illness, no diagnosis had been made and no cause of the purpura had been found.

On physical examination the patient presented a striking appearance (fig. 1). The skin about the eyes was diffusely purpuric, resembling bilateral "black-eyes." The tongue protruded from the mouth and was thick, red, and gelatinous in appearance. Hemorrhagic vesicular lesions were present in the oral mucous membranes and the lips were purpuric. Extensive hemorrhagic lesions were present symmetrically in the axillae, about the breasts, in the groins, on the thighs and in the region of the vulva. The skin of the axillae was thickened and brawny. The skin lesions in general consisted of hemorrhagic vesicles and bullae.
ATYPICAL AMYLOIDOSIS WITH NONTHROMBOCYTOPENIC PURPURA

1. —Case 1. Periorbital purpura and marked macroglossia.
2. —Case 2. Marked discoloration and soft tissue swelling of hands.

Some of these had ruptured and exposed the underlying dermis. On the fingers, especially, and on the toes and elbows, soft, purplish, cutaneous and subcutaneous swellings were present (fig. 2). There was no lymphadenopathy or enlargement of liver or spleen. The blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. The heart was enlarged and an apical systolic murmur was present. The cardiac rhythm was regular. Rales were heard at both lung bases. Brawny edema was present in both legs.
Laboratory studies were as follows: hemoglobin 9 Gm. per 100 cc., red blood cells 2,300,000 per cu. mm., hematocrit 29 cc. per 100 cc., white blood cells 5000 per cu. mm., with 50 per cent segmented neutrophils, 6 per cent basophils and 44 per cent lymphocytes. The urine was normal on repeated examinations and no Hance Jones protein was found. The blood Wassermann test was negative. The serum albumin was 2 Gm. per cent and globulin 2.2 Gm. per cent. Studies for the presence of cryoglobulins were negative. The fasting blood sugar, nonprotein nitrogen, alkaline phosphatase, and vitamin C blood levels were normal. A Congo red test showed 27.6 per cent of the dye removed from the blood in 1 hour. Bleeding time, Lee-White clotting time, clot retraction, platelet count, and prothrombin time were all within normal limits. The tourniquet test for capillary fragility was moderately positive. Blood cholesterol was 352 mg. per cent with esters 272 mg. per cent. Blood uric acid was 4.2 mg. per cent. A bromsulfalein test, 5 mg. per Kg., was normal. Two basal metabolism tests were minus 7 and minus 3 per cent. The electrocardiogram had low QRS complexes with flat T waves in the precordial leads, and was interpreted as showing nonspecific myocardial changes. Roentgenograms of the chest, long bones and skull, large intestine, stomach, and gall bladder were normal. An x-ray of the spine revealed wedging of the sixth and seventh dorsal vertebrae. Further inquiry elicited the history of an old spinal injury which was consistent with the x-ray appearance of the vertebrae. Skin biopsies of the peculiar soft-tissue finger and toe swellings were reported as showing marked infiltration of the dermis and subcutaneous tissue by a dense hyaline material compatible with the changes in myxedema. Focal hemorrhages were observed in this tissue.

Sternal marrow aspiration was performed two days after admission. This revealed a marked increase in plasma cells, chiefly of mature type. The cellularity was low normal. Megakaryocytes were normal. There was a moderate reduction in the number of cells of the granulocytic and erythrocytic series with no defect in maturation. The diagnosis was

Fig. 3.—Case 1. Particle smear of sternal marrow aspirate showing replacement of normal marrow elements by plasma cells. Obtained shortly after admission. (X 800.)

Fig. 4.—Case 1. Smear of gross amyloid from sternal aspiration. Nests of plasma cells present. (X 800.)

Fig. 5.—Case 1. Particle smear of sternal marrow aspirate obtained near end of illness. Diffuse plasma cell infiltration. (X 800.)
ATYPICAL AMYLOIDOSIS WITH NONTHROMBOCYTOPENIC PURPURA

that of abnormal marrow consistent with plasma cell myeloma. A second marrow aspiration was carried out fifteen days later. This showed normal cellularity. Cells of the erythroid and granulocytic series were markedly reduced. Megakaryocytes were normal. Particle smears showed sheets of plasma cells replacing normal marrow elements to a pathologic degree (fig. 3). These plasma cells were chiefly mature and not dysplastic. Rare plasmoblasts were present. The marrow diagnosis was plasma cell myeloma or aleukemic plasma cell leukemia.

Because of the electrocardiographic changes and the report of the skin biopsy, the patient was first treated with thyroid extract. No improvement was obtained. A course of urethane was then given, starting with 0.3 Gm. three times daily. When the dosage was raised to 3 Gm. daily the white cell count fell to 1850 per cu. mm. Marrow examination then showed a marked reduction in cellularity with very few mature granulocytes. Megakaryocytes were normal but cells of the erythrocytic series were reduced and plasma cells were also diminished when compared to the previous marrow aspiration. Some improvement in the clinical picture was observed. The urethane was withheld until the white count improved and was then tried at a dosage of 0.25 Gm. three times daily. After one week the white cell count dropped from 4800 to 2750 per cu. mm. and the drug was again discontinued. Two blood transfusions were given.

In December 1949, four months after admission, the patient was completely restudied. X-rays of the shoulders, ribs, long bones, and pelvis showed no bony change. Serum proteins were low, 3.5 Gm. per cent, with albumin 2.4 and globulin 1.1 Gm. per cent. The urine contained 2+ albumin but no Bence Jones protein. The blood nonprotein nitrogen was normal. Alkaline phosphatase, percentage of cholesterol esters, serum bilirubin, and thymol turbidity tests were normal. Sternal marrow aspiration revealed low normal cellularity with marked reduction in the granulocytic and erythrocytic series and abnormal increase in plasma cells.

The patient continued to be severely ill. Transfusions of whole blood were given in the fifth, sixth, and ninth months after admission. Sternal marrow examination in the ninth month of hospitalization revealed normal cellularity with an abnormal increase of plasma cells. Megakaryocytes were normal and the granulocytic and erythrocytic series were complete but reduced. Cortisone was administered at a dosage of 100 mg. daily from June 20 to June 27 without clinical improvement. Sternal marrow aspiration performed on June 27 showed a remarkable finding. In addition to the usual bloody fluid, a large amount of a yellowish, gelatinous material was obtained. This was the first time we had ever observed such a substance in a marrow aspiration. Particles of this gel were smeared on cover slips and stained by Wright's stain. The preparations showed a diffuse, homogeneous, magenta, metachromatic substance in which portions of marrow stroma and plasma cells were observed. The plasma cells were present discretely and in small nests or focal collections (fig. 4). Smears of marrow particles selected from the bloody portion of the aspirate revealed a high normal cellularity. Abundant cells of the granulocytic, erythrocytic and megakaryocytic series were observed with no defect in maturation. An abnormal number of plasma cells were seen. A Congo red test performed two weeks later showed 86.7 per cent removal from the blood in 1 hour.

The macroglossia became so extreme that the patient was unable to swallow. The skin lesions broke down and became infected. The patient developed abdominal pain and a large ecchymosis appeared at the navel which suggested intra-abdominal hemorrhage. She received further transfusions, and parenteral fluids. ACTH was tried without effect. A final sternal marrow aspiration on August 8, 1950, twelve months after admission, showed diffuse plasma cell infiltration, chiefly of mature, relatively normal appearing cells (fig. 5). The Congo red test two days later revealed only 22.2 per cent removal in 1 hour.

The patient developed pulmonary edema and died on August 18, 1950, after more than a year of continuous hospitalization and four years after the onset of symptoms.

At autopsy, widespread gross pathologic changes were evident. The tongue was so en-
larged, thickened, and hemorrhagic that it filled, and even protruded from, the oral cavity. The lips were markedly swollen and protuberant. Both legs were swollen and exhibited pitting edema up to the knees. The skin showed multiple lesions. There were marked, soft, purplish swellings of the tissues of the tips of the fingers, the toes, and about the elbow joints. These partially covered the nail beds of the fingers and toes, and formed fibromulike masses over the elbows. About the eyes and mouth, over the chest, abdomen, almost the entire back, and the anterior surfaces of the legs, were numerous large ecchymoses over which the skin could easily be broken. In many places the skin actually was ulcerated and exuded profuse amounts of thick, yellowish fluid. There was such marked edema of the vulva and the tissues of the inguinal regions that the skin was fragile. Large amounts of a mucoid, sticky material were present in the subcutaneous tissues.

In the peritoneal cavity, zones of serosal hemorrhage were found in the small intestine and colon. Similar hemorrhages were present in the epicardium. The pleural and pericardial cavities contained increased amounts of clear serous fluid. The heart weighed 300 Gm. The epicardial fat was thick and contained a gelatinous fluid while the underlying muscle tissues were soft, flabby, and of a muddy brown color. The lungs were focally atelectatic in the lower lobes but were otherwise negative. The spleen and liver were not remarkable. Focal hemorrhages were found in the gastric mucosa and in the deeper portions of the wall of the small and large intestine. The kidneys were of normal size but their cortices appeared pale. Hemorrhagic areas were present in the endometrium of the uterus and the cervix was diffusely hemorrhagic. The skull showed no unusual lesions. The marrow of the femur, the ribs, the sternum, and several vertebral bodies appeared slightly pale brown in color. No bony lesions were observed.

Histologically, the most striking changes were found in the stromal and perivascular tissues of many organs. In the epicardium, myocardium, and endocardium, deposits of a pinkish, hyaline material were present in abundance. In the epicardium, the hyaline deposit formed thick bands about veins and venules and was sometimes present in arterial walls, though in smaller amounts. It occurred also in irregular patches throughout the fat tissue, sometimes in such quantities that the fat cells were compressed or obliterated. In several of these areas acute hemorrhages were present. The fat tissue which was not infiltrated with the hyaline material showed serous atrophy. The deposits in the myocardium were chiefly in the stromal tissues but in places they were of such size as to compress and cause atrophy and disappearance of muscle cells. In the subendocardial regions large amounts were deposited and some papillary muscles were practically replaced by hyalin. In the aorta the hyaline accumulations were chiefly in the subendothelial regions and some papillary muscles were practically replaced by hyalin. Indeed, individual muscle cells were often widely separated from each other by the hyaline interstitial substance. Here and there focal hemorrhages were present.

The deposits in the lungs were striking and abundant in the walls of both pulmonary arteries and veins, even to their smallest branches, and irregularly distributed in the alveolar walls. In the latter situations many capillaries appeared to be obliterated and the hyaline accumulations resembled minute balls, nodules, or structureless linear bodies covered by a thin cellular membrane that separated the deposits from the alveolar spaces. Vessel lumens were greatly reduced in size and alveolar spaces were generally smaller than normal. Even the visceral pleura contained hyaline masses.

In the spleen, hyaline deposits were few and inconspicuous, being found only in the capsule and in some trabeculae. The gastrointestinal tract, however, contained large deposits, chiefly in the submucosa and muscularis, where they formed thick layers about thin-walled veins or spread out in nodule-like fashion into the smooth muscle. Indeed, individual muscle cells were often widely separated from each other by the hyaline interstitial substance. Here and there focal hemorrhages were present.

The pancreas and liver were little affected. However, careful examination of the latter organ showed that, in narrow spaces between the lining cells of the hepatic sinusoids and the liver cell cords, small accumulations of a smoky-appearing, vaguely hyaline material were present. These were believed to be deposits of the same material as that found in abundance elsewhere.

In the periadrenal tissues large deposits were present about veins and in the fatty stroma but the adrenals themselves were not involved. In the kidneys practically all glomeruli...
Fig. 6.—Case 1. Blood vessel in subcutaneous tissue. Marked deposition of amyloid throughout. (X 300.)

Fig. 7.—Case 1. Hemorrhage in subcutaneous tissue about vessel showing apparent rupture. Tissue is extensively replaced by amyloid. (X 300.)

contained at least some hyaline material, from minute ball-like deposits to quantities that practically replaced the tufts. In the bladder, as in the intestine, large amounts of hyaline material were present, not only about small vessels in the mucosa and submucosa but also as muscle-destroying or muscle-replacing masses deeper in the vesical wall. Small accumulations were found in the uterus but none was found in the ovaries.
The skin, subcutaneous tissues, skeletal muscles, and the tissues of the tongue were markedly and diffusely infiltrated by the hyaline material, as were the stroma and surrounding tissues of lymph nodes from various locations. In the skin the deposits reached up to the basal layer of the epithelium and often spread diffusely throughout the dermis, forming thick, hyaline walls of little blood vessels that persisted only as narrow slits containing red cells. Hemorrhages were frequent (figs. 6, 7). Sections from the tongue were stained for amyloid but the hyaline material failed to give the characteristic tinctorial reaction for this substance. However, the diffusely scattered nature of the deposits, their predominantly subendothelial and perivascular locations, and the involvement of organs usually affected in primary amyloidosis, led us to conclude that the deposits were, in fact, amyloid of a type similar to that found in primary amyloidosis.

The bone marrow was normally cellular in most areas. Focal deposits of amyloid were present. A diffuse increase in plasma cells was seen. Occasional grouping of a few cells but no sheets of plasmocytes were found. Normal marrow elements of the granulocytic, erythrocytic, and megakaryocytic series were observed in adequate numbers.

Case 2

G. D., a 59 year old white female, was admitted to the Albany Hospital on January 14, 1950, because of extensive skin purpura of two years' duration, involving the periorbital tissues, breasts, and thighs predominantly. She also complained of a troublesome cough for one year. The skin lesions were first noticed in 1948. Studies carried out by a hematologist at that time, which included marrow aspiration, had revealed no findings of diagnostic significance.

The patient did not appear seriously ill. There were moderate hemorrhagic lesions about the eyes and on the breasts and thighs. These consisted of small areas of purpura with hemorrhagic vesicles, in the epidermis. The skin showed increased pigmentation about the purpuric regions. Physical examination was otherwise not remarkable. Sternal marrow aspiration, performed three days after admission, revealed an abnormal increase in plasma cells in particle smears, with focal areas showing complete replacement of normal elements by cells of the plasmocytic series. Complete blood counts were normal. Bleeding time, Lee-White clotting time, prothrombin time, and platelet count were normal. There was a slight increase in capillary fragility by the tourniquet test. Urinary Bence Jones protein was absent, serum proteins were normal, and x-rays of the skull, spine, pelvis, and long bones were normal.

The patient was discharged on January 25, 1950. She was placed on urethane therapy, consisting of 1 Gm. three times daily for four weeks, and 2 Gm. three times daily for another four weeks. This drug had no effect on the purpura, the peripheral blood, or the marrow aspirate. Because of the persistence of the patient's symptoms she again consulted the hematologist who had examined her originally. He was unable to confirm the marrow finding of plasma cell hyperplasia. The marrow smears which he prepared were later examined by one of us (S. P.) and were found to contain no particle material. They showed only a thin spread of normal marrow elements.

The patient continued to have purpura and also developed more severe coughing attacks which were associated with wheezing respirations of asthmatic type and dyspnea. Musical and coarse rales were heard in both lungs. She suffered from anorexia and gradually lost strength. Finally dependent edema developed which did not respond to salt restriction, administration of ammonium chloride, or mercurials given orally and parenterally. She returned to the hospital on September 11, 1951, twenty months after her first admission.

Physical examination now revealed a dyspneic, chronically ill woman with striking purpuric lesions. These were bullous in many areas and involved the periorbital tissues in a peculiar "eye-glass" distribution (fig. 8). They were present on the breasts, lower abdomen, and thighs. Moderate macroglossia was present. Dullness and rales were noted in both lung bases. There were no cardiac murmurs or irregularities of rhythm. The blood pressure was 100 mm. Hg systolic and 80 mm. diastolic. There was marked pitting edema over the sacrum and in the lower extremities.

Laboratory studies on admission revealed: hemoglobin 11.0 Gm. per 100 cc., red blood
Electrophoretic studies were performed at the laboratory of Dr. D. H. Moore, Columbia University, College of Physicians and Surgeons, New York, N. Y.
X-ray was reported as showing a peribronchial, nodular infiltrate involving both lung fields suggesting the possibility of a pleural and parenchymal infiltration, leukemic in character. X-rays of the pelvis and skull showed a mild generalized demineralization of all the visualized bony structures, without evidence of destructive changes. Alkaline phosphatase was normal. Liver function studies were normal except for bromsulfalein retention of 16.1 mg. (5 mg. per Kg. test). An electrocardiogram was reported as presenting nonspecific changes, with P-R interval at the upper limit of normal and low voltage in the limb leads and in V1, V5, and V6.

Fig. 9.—Case 2. Section of skin biopsy. Extensive deposition of amyloid and hemorrhage. (X 96.)

Fig. 10.—Top central area of figure 9. Marked dermal amyloid deposit and hemorrhage. The epidermis is also involved. (X 480.)
ATYPICAL AMYLOIDOSIS WITH NONTHROMBOCYTOPENIC PURPURA

A skin biopsy of a hemorrhagic area on the left breast was most interesting. It showed extensive epidermal and dermal deposition of a hyaline substance resembling amyloid (figs. 9, 10). Tinctorial tests for amyloid with crystal violet were negative.

Sternal marrow aspiration was repeated on September 28, 1951, one year and eight months after the patient's first admission. Accompanying the usual gross aspirate was a large amount of yellowish, gelatinous material. This was exactly like the gel obtained from the marrow of M. T., case 1. Smears of this substance stained by Wright's stain showed it to be a magenta staining, homogeneous material in which small nests of plasma cells were present. Smears of marrow particles were normally cellular. There was an abnormal increase in plasma cells and nests or focal collections of these cells were observed. The plasmocytes were consistent in appearance with myeloma cells but bizarre or unusual forms which may be seen in this disease were not observed.

The patient was treated for congestive heart failure by digitalization, low sodium diet, thiamin chloride, and thoracentesis. She responded poorly. The predominant problems were the extensive purpura and heart failure. The skin lesions broke down and, despite supportive therapy, the patient became progressively weaker and developed diarrhea, rectal bleeding, and vomiting. She died on December 19, 1951, four years after the onset of her illness.

At autopsy the body appeared poorly nourished and showed evidence of marked wasting. The skin was dry and inelastic. Many small petechiae and large, irregular subcutaneous hemorrhages were present about the eyes, on or beneath the breasts, in the groins, and over the buttocks. Small superficial ulcers and areas of hyperpigmentation were observed in these regions.

The peritoneal cavity contained 1000 ml. of clear yellowish fluid. The omentum was very unusual. It was a peculiar pink color and contained many minute grayish yellow nodules, measuring 0.1 cm. in diameter. Similar nodules were present in the serosa of the moderately distended stomach. Each pleural cavity contained 700 ml. of clear straw-colored fluid but the pericardial cavity contained only 5 to 10 ml.

The heart weighed 320 Gm. and was generally firmer and more rigid than normal. The auricular walls in particular failed to collapse and maintained their distended form in unusual fashion. The epicardium contained only a small amount of edematous fat. Adjacent to many of the smaller blood vessels were distinct, pale, pinkish zones which encircled vessels cut transversely or ran parallel to those incised longitudinally. On section, the myocardial tissues were pale brown in color and had a waxy texture. In the interventricular septum and the posterior left ventricular wall about two thirds of the thickness of the myocardium appeared unusually firm and remarkably homogeneous, distinctly different from the adjacent, more normal myocardium. In many situations pinkish-red rings surrounded the vessels or accompanied them for considerable distances. Unquestionably this red material was Congo red dye which had been given to the patient during life and was now held in amyloid deposits about blood vessels.

Histologically, the deposition of amyloid was very extensive. The hyalin material was present in large amounts about veins and venules in the epicardium where it was associated with minute hemorrhages into the surrounding fat. In the interstitial tissues amyloid occurred between fat cells and formed small nodular accumulations in fibrous stroma. The hyalin was observed in the myocardial tissues, where it was deposited diffusely between muscle fibers, in the walls of small veins, and as large nodules in the interstitial stroma. These nodular masses actually resembled the amyloid tumors occasionally found in the larynx. Some were large enough to cause pressure atrophy of adjacent or surrounded muscle fibers. In general, arterial walls and endocardium were only slightly involved.

The lungs were large and voluminous, the right weighing 980, the left 820 Gm. The pulmonary tissues, especially of the lower lobes, were firm and doughy and when pressed upon retained the depression. The histologic changes in these organs were remarkable. Interstitiolar walls were diffusely and thickly infiltrated while the alveoli were either diminished in size or obliterated by accumulations of amyloid. Capillaries were flattened or compressed

* Those who are interested in description of these cells are referred to the paper by Propp, et al. 5
and veins were surrounded by hyaline material which not only extended into the surrounding stroma but also greatly reduced the size of their lumens. Arteries were similarly but less extensively affected. Small hemorrhages were observed in only a few areas (fig. 11).

Amyloid was present in minimal amounts in the spleen, mainly about veins and in the region of an old infarct. In various parts of the gastrointestinal tract, however, large quantities of the pink-staining hyaline material were seen in all coats but the mucosa. Deposits were chiefly about veins and venules, though many arteries were slightly affected. Some of
the venous perivascular accumulations were extremely thick. Varying amounts of amyloid were observed in the muscular coats, either as small nodules or as diffuse collections between muscle cells. Many of these cells showed evidence of compression atrophy. The acinar and islet tissues of the pancreas were well preserved. The stroma, however, was increased and contained large amounts of hyaline.

Amyloid deposits were minimal in the liver, being found chiefly about portal venules or in minute, punctate collections beneath the endothelial linings of some of the sinusoids. In the adrenals, too, amyloid deposits were rare but they occurred in abundance about venules in the periadrenal fat. The adrenal cortical cells appeared well-vacuolated.

Renal deposits of amyloid were moderate in amount and occurred chiefly about venules in the cortices and in the walls of some arterioles. Glomeruli were generally not involved. Hyaline accumulations were more abundant in and around an old infarct. In the bladder wall the amyloid formations were more numerous, being present about blood vessels as well as irregularly in the muscular coat and diffusely in the serosal fat.

The tongue was thickened by large, round or oval, amyloid-tumor-like deposits. These were most numerous in the subepithelial regions but smaller accumulations were present in, and caused pressure atrophy of, the muscles of the tongue. Small perivascular deposits were also found in the thyroid gland.

Bone marrow changes were unusual and remarkable. In sections from various sites the hematopoietic tissues and the normal adipose stroma were almost completely crowded out and replaced by diffuse formations of amyloid (fig. 12). In some situations blood-forming tissues were absent and the fat cells could be recognized only as round or oval spaces in the diffuse structureless deposit. In other sections, however, hematopoietic tissue could still be observed. This consisted of small or large groups of cells among which only a few were recognizable as normoblasts, myelocytes, and megakaryocytes. The majority of the cells were not readily identified but many of them were plasma cells. Everywhere in the bone marrow, spreading diffusely throughout the normal fatty stroma like a gelatinous infiltrate, were the massive accumulations of amyloid.

DISCUSSION

The clinical picture presented by these two patients, consisting of chronic nonthrombocytopenic purpura of unusual type and distribution, associated with generalized amyloidosis and plasma cell hyperplasia of the bone marrow, is sufficiently distinctive to constitute a rare and unusual syndrome. The lack of any other clinical, laboratory, or x-ray evidence of plasma cell myeloma during four years of observations, and the marrow aspiration of gross deposits of amyloid containing nests of plasma cells contribute to make this syndrome more remarkable.

The problem of diagnosis does not appear to have been resolved even after postmortem study. It is clear that re-examination of our criteria for diagnosis of plasma cell myeloma, and primary amyloidosis, is indicated.

Amyloid disease is generally divided into four major categories. The most common of these is secondary amyloidosis which affects the spleen, liver, adrenals, kidneys, and blood vessel walls, and is usually associated with chronic suppurative disease. The second is primary amyloidosis, which classically involves the mesodermal tissues. This form is rarely diagnosed antemortem because of its peculiar clinical manifestations. The third form of amyloidosis, that found in association with myeloma, generally has the distribution and staining reactions of the primary type. Amyloidosis with myeloma has been extensively studied by Atkinson. Its similarity to primary amyloidosis is so striking that Lichtenstein and Jaffe have suggested that whenever amyloid is found in unusual sites the possibility of myeloma should be considered. The
fourth variety of amyloid is localized and nodular, and consists of focal amyloid deposits (so-called “amyloid tumors”). It should be noted that whereas secondary amyloid usually stains with Congo red and exhibits metachromatic staining, primary amyloid, and amyloid associated with myeloma, often do not have these staining qualities. This type of hyalin has been called paramyloid.

Primary systemic amyloidosis is a rare disease. Eisen confirmed two cases and reviewed forty-six others, making a total of forty-eight cases up to 1946. Dahlin reported six cases and tabulated a total of fifty-seven from the literature. Higgins and Higgins reported on one patient with primary amyloidosis and reviewed a total of seventy-one cases collected from the literature. Since then we have been able to find six individual case reports, one group of fifteen cases, and one report of two cases. In only one of these reports was there any observation of abnormal plasmacytosis in the bone marrow.

The clinical picture of primary amyloid disease has been well described by Eisen. Notably, only eight out of forty-six patients were diagnosed antemortem. Congestive heart failure of intractable nature was present in 54 per cent of the patients. Ballinger stressed the concept that the findings of intractable congestive failure without obvious valvular disease, hypertension or coronary sclerosis, and with a nonspecific electrocardiogram, should suggest a diagnosis of amyloid heart disease. Macroglossia was found in 42 per cent of Eisen’s series. In a recent article this finding was emphasized as a clinical clue to the diagnosis of amyloidosis although it was present in less than half of the patients. Dahlin’s review of the pathology of this disease in fifty-four autopsied cases revealed cardiac involvement in forty-six, lung infiltration in twenty-four, and skin amyloid in thirteen patients. Amyloid was present in the tongue in twenty-six and in the gastrointestinal tract in thirty-three cases.

The predominant complaint of the two patients described in the present report was purpura. We are postulating that this purpura was secondary to amyloid infiltration of the tissues and blood vessels and it is our opinion that primary amyloidosis, as well as that associated with myeloma, should be added as a cause of the already complicated group of vascular purpuras. In a general review, Frommeyer and Epstein presented a classification of purpura in which there was no mention of amyloidosis. This omission was also observed in modern textbooks of hematology. However, purpura in systemic amyloidosis is not uncommon. Eisen found it in 21 per cent and Higgins and Higgins in 15 per cent of the cases. Dahlin reported one case of purpura which was considered to be due to vascular involvement with amyloid. Moschowitz described one patient with amyloidosis who had purpura of the oral mucosa and eyelids. Strauss, in 1933, reported on purpura due to amyloid involvement of the blood vessels. A Cabot case, in the New England Journal of Medicine, described a patient with purpura which involved the eyelids in whose intestinal mucosa vessels were found which were infiltrated with amyloid. The suggestion was made that Henoch’s purpura might occasionally be confused with purpura due to primary amyloidosis. Pearson, et al. reported a case of amyloidosis with petechial hemorrhages under both eyes. One additional case of purpura was reported by Parker and his associates. Recently, Goltz reviewed in detail the skin and mucous membrane manifestations of systematized amyloidosis and
reported two cases. He stated that the most common cutaneous lesion is hemorrhage into the skin. This occurs most frequently in the body folds, and the eyelids are often an early site. An illustration of his first case is remarkably similar to the two patients being reported. The bone marrow aspiration in Goltz' first patient revealed 6 per cent plasma cells which were said to be "not of a neoplastic type." Unfortunately no description of the bone marrow was given in the postmortem examination. In the second patient sternal bone marrow examination showed 23 per cent plasma cells and some amorphous material was described in the marrow "which did not take stains for amyloid." Autopsy was not obtained on this patient.

The possibility that cryoglobulinemia might have caused the purpura in the cases being reported was considered. Cryoglobulinemia as a cause of purpura was first emphasized by Lerner and Watson. They described a patient who had extensive purpura following exposure to cold whose blood serum contained a protein which was precipitated by cold. Lerner and Watson suggested the term of cryoglobulin for any one of a group of proteins with the common property of precipitating or gelifying from cooled serum and also for those proteins which may precipitate at room temperature in high concentration. Barr, Reader, and Wheeler have reported a second patient with purpura associated with cryoglobulinemia and have discussed this problem at length. They suggested that error in obtaining total serum proteins and albumin and globulin fractions might be avoided if the blood specimen is kept at 37 C. until the estimation of protein is performed. In each of our patients, serum protein values were obtained on two specimens of blood drawn at the same time, one of which was examined shortly afterward and the other after remaining at refrigerator temperature overnight. No difference in values of proteins were obtained. No precipitation was noted in the serum after exposure to refrigerator temperatures. There was no history of exacerbation of purpura after exposure to cold and indeed purpura was constant and progressive in these patients in the hospital, and during the summer months. Raynaud's phenomenon, which has been described as being associated with cryoglobulinemia, did not occur in either of our patients. No gel formation was observed in the heart or blood vessels of our patients upon postmortem examination. We have observed extreme gel formation in the blood of one patient, during life and at postmortem examination, who had plasma cell myeloma with a very high serum globulin. This patient had shown no purpuric lesions (case). The antemortem aspiration of grossly recognizable amyloid from the marrow in the two cases being reported is a most remarkable phenomenon. Diffuse amyloid infiltration of the marrow observed at postmortem examination has been described. Trubowitz in 1950 reported a case in which an eosinophile, amorphous material was noted microscopically in smears of sternal marrow aspirate stained by Wright's and Giemsa stains. This material was considered to be amyloid (no metachromatic staining was reported). No abnormality of the gross marrow specimen was noted. He also described globules within leukocytes which he felt were amyloid globules. Some of these leukocytes containing amorphous material strongly resembled the L.E. cell. Postmortem examination in this case revealed multiple myeloma and diffuse amyloidosis. This was be-
heved to be the first case in which amyloid was aspirated from the marrow antemortem. We have been unable to find any report in the literature on marrow aspiration of grossly visible amyloid.

Marrow plasmocytosis, other than that due to myeloma or plasma cell leukemia, associated with a primary type of amyloidosis, is an unusual finding. Recently, examples of plasma cell reactions in the bone marrow have been described in several conditions and confusion with myeloma has been demonstrated. Barr, in a recent editorial, has discussed the relationship of the plasma cell to hyperglobulinemia and hypersensitivity in general. The concept of the relationship of the plasma cell to antibody formation, was described in detail by Fagraeus in 1948. Robertson reported two cases of plasmocytosis of the marrow in which sulfonamides had been given. He attributed the plasmocytosis to a sensitivity to this drug. Postmortem examination showed a generalized tissue plasma cell reaction. His second case was believed to be atypical myeloma before autopsy. Robertson stressed the difficulties encountered in differentiating a nonspecific plasmocytosis of the marrow from myeloma. Carter described an interesting case, in which there was an elevated serum globulin, which was thought to be myeloma. At autopsy, trichinosis was found and the marrow showed a marked plasmocytosis. Ritama’s case was one of hyperglobulinemia and plasmocytosis of the marrow in which primary amyloidosis was diagnosed postmortem. The unusual findings in this patient were thought to be due to a peculiar type of immune reaction. Baker, et al. reported a case of primary amyloidosis which was confused with myeloma because of a plasma cell reaction present in a biopsy specimen of a lymph node. One wonders whether in the above two patients the diagnosis was actually plasma cell myeloma concealed by the amyloid infiltration. Bayrd and Bennett, in a discussion of amyloidosis complicating myeloma, stated “Occasionally, a tumor of amyloid will obscure the underlying plasmacytoma within which it has arisen, and at other times, it may appear to be a primary process as histologic sections of the bones fail to disclose a diffuse multiple myeloma which smears will have revealed.”

The bone marrow aspirations in the cases reported in this paper were extensively studied using a technic recently described in detail. The value of the use of particle smears was clearly demonstrated in the second patient who had two negative reports on marrow aspirations performed by direct slide smear technic. The demonstration of plasma cells in nests and sheets and discretely in bone marrow aspirate is greatly facilitated by the use of well-prepared marrow particle smears. This point was emphasized previously in the article describing this technic.

The importance of skin biopsies in the diagnosis of paramyloidosis, particularly in association with purpura, is obvious in these cases. Skin biopsy should certainly be performed on obscure cases of chronic purpura in an effort to ascertain the mechanism of the hemorrhagic state.

Summary

1. Two cases of chronic nonthrombocytopenic purpura of unusual distribution, associated with generalized amyloidosis and plasma cell hyperplasia of the bone marrow, are described in detail with their postmortem findings.
ATYPICAL AMYLOIDOSIS WITH NONTHROMBOCYTOPENIC PURPURA

2. Grossly recognizable amyloid was present in the antemortem sternal marrow aspirates of both patients.

3. Skin sections in each patient revealed hemorrhages associated with marked amyloid deposition in the dermis and blood vessel walls. It is postulated that this purpura was of vascular type.

4. The diagnosis of the underlying pathology in both patients was made possible by marrow aspiration. The importance of proper use of marrow particle smears in the diagnosis of plasma cell disturbances in the bone marrow is emphasized.

5. The difficulty in differentiating plasma cell myeloma from other causes of plasma cell hyperplasia of the marrow is clearly documented in this report.

SUMMARIO IN INTERLINGUA

1. Es presentate un description detaliate de duo casos de chronic nonthrombocytopenic purpura distinguite per su distribution inusual e associate con amyloidosis generalisate e hyperplasia del cellulas plasmatic del medulla ossee. Etiam le constatationes necroptic es describite.

2. In ambe patientes aspiratos de medulla sternal monstrava grosse quantititates de amyloide.

3. Sectiones dermic del duo patientes revelava hemorrhagias associate con depositos marcate de amyloide in le derma e le parietes del vasos sanguinari. Nos postula que iste purpura esseva del typo vascular.

4. Le diagnose del pathologia causal in ambe patientes esseva facite possibile per aspirationes medullari. Es sublineate le importantia de correctemente usar le technica del frottis medullari in diagnosticar disordines del cellulas plasmatic in le medulla ossee.

5. Iste reporto presenta un clar documentation del difficultate de differentiar inter myeloma del cellulas plasmatic e altere causas de hyperplasia medullari del cellulas plasmatic.

REFERENCES


Atypical Amyloidosis Associated With Nonthrombocytopenic Purpura and Plasmocytic Hyperplasia of the Bone Marrow

SIMON PROPP, WILLIAM B. SCHARFMAN, RICHARD T. BEEBE and ARTHUR W. WRIGHT