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**A CASE OF PLASMOCYTOMA
ASSOCIATED WITH BENCE-JONES
PROTEIN.**

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Adelaide Hospital.

IN 1847 Bence-Jones described the characteristics of a protein substance which appeared in the urine in a case of osteomalacia fragilis rubra.

J. Von Rustizky, in 1873, outlined the disease known as "multiple myelomata," regarded as a neoplasm of the bone-marrow, having its origin in the blood-forming cells, and which, in the course of its growth, tends to replace the true bony substance.

Kahler, in 1889, was the first to associate Bence-Jones protein with bone marrow tumours. Up to 1917 over 200 cases of Bence-Jones protein occurring in the urine have been reported, and the greater number of these cases (approx. 80 per cent.) have been associated with "multiple myelomata."¹

It is also stated to have been found in lymphatic and myeloid leukemia, myxœdema, exophthalmic goitre, carcinoma, nephritis, hypertension, etc.

¹ Walters. Journal A.M.A. 5. 4. 1921.

Further cases of multiple myelomata have been described in which there was no Bence-Jones protein detected in the urine. Therefore, so far as the evidence goes, multiple myelomata and Bence-Jones proteinuria do not necessarily coincide in the same case, but the presence of this particular form of protein in the urine is strongly suggestive of bone-marrow disease.

The following case is one with many points of interest:—

On January 19th, 1921, Mr. E. M., aet 44, was admitted into the Adelaide Hospital. He was unable to stand or walk. He appeared very anemic—his pallor being like that of a case of pernicious anemia. He complained of very severe pain down the outer side of his right leg, of weakness, and also that his tongue was so sore that he could not swallow solid food. His weight on admission was 131 lbs., and he stated that he had been 168 lbs. He had served in the army from 1916-1919, and since his discharge had been acting as a gamekeeper. His family history was unimportant, and he himself had been strong and healthy up to October, 1920, when he began to suffer from intermittent attacks of pain in his right leg, which radiated generally from the ankle region towards the thigh. These attacks of pain were always more severe during the night, and as they gradually became more frequent, he remained in bed, being in practically continuous pain. His tongue commenced to swell; his swallowing became very difficult and at times impossible, and he got progressively weaker. On his admission to the Hospital he was very thin, especially his lower limbs, and his eyes were sunken, his cheek bones prominent, and he appeared to have very little subcutaneous fat. He had slight right lateral scoliosis. On palpating him myriads of small, millet-sized tumors were felt under the skin—some of these moved with the skin, others did not. They were quite universal. His tongue was very swollen and extremely hard. It was indented by his teeth, which were in a carious condition, and he was unable to protrude it more than quarter of an inch. There was a slight ulcer on its right antero-lateral border. He had a faint basal systolic bruit, low B.P., and slightly atheromatous arteries.

Lungs.

These were fairly clear, but on February 12th slight dullness was found in both bases, and there was a small area of superficial œdema in his right axilla. He also complained more of pain in his ribs.

Abdomen.

This was curiously doughy on palpation, but otherwise normal.

Nervous System.

Plantar and eye reflexes normal; epigastric reflexes absent; knee-jerks exaggerated on admission; Babinski sign present in left foot; no ankle nor patellar clonus; marked hyperæsthesia in his feet; heat, cold pain, sense of position, localisation, etc., unimpaired; light touch impaired below both knees.

Skeleton.

He had marked bony prominences at the angle of each mandible, conical in shape, that on the right side being the larger. Both mastoid processes were irregularly enlarged. There was much thickening in the region of the chin and marked unevenness of the sacro-iliac joints. He was remarkably tender on percussion over the pelvis generally, and also over the ribs.

Blood.

R.B.C. 3,500,000; white cells, 12,000; differential count, P. 58%; Lym, 40%; Hb. 60%. Wassermann reaction negative. His blood serum was milky in appearance, and contained the Bence-Jones protein; 20 ccms. of blood was sent for laboratory examination.

Urine.

The daily amount averaged 35 oz., with a S.G. varying from 1,016 to 1,022 being acid in reaction. It was milky on being passed, and gave the characteristic Bence-Jones reaction. On heating a ppt. appeared at 44 degs. C., becoming very flocculent, this cleared on further heating (80 degs. C.) and reappeared on cooling. This ppt. was greatly increased by adding common salt to the urine before heating. The nitric acid test gave a very definite ring which almost disappeared on heating and returned on cooling.

With hydrochloric acid this was better shown, but a purplish colour was developed on heating.

Dilute hydrochloric and dilute sulphuric acids gave a ring test.

Diluted urine was more sensitive and showed all the reactions much clearer, as there was a slight amount of ordinary albumen. Examination of the sediment showed it to be principally Bence-Jones protein, and on one occasion urates were precipitated on top of the protein.

Under the microscope the sediment showed long, thin masses of crystalloid forms not very well defined. The sediment gave positive Biuret reaction.

Dr. Walter G. Smith kindly sent me the following note:—

(a) The protein sediment from your case showed, under the microscope, rounded and indistinctly crystalloid forms.

(b) The protein is precipitated by dilute HCl or H_2SO_4 .

(c) The solubility of the primary heat precipitate at 100 degs. is probably due to a labile molecular compound with the urinary salts, which is dissociated upon cooling (Hopkins and Savory).

(d) The sediment gives the ordinary protein reactions, but the yield of aromatic amino-acids is high (Hopkins and Savory).

A provisional diagnosis of cancer of the pelvis was made, his tongue and skin conditions being undetermined. The first x-ray report of pelvis on 25/1/21 was—"General rarefaction of pelvic bones. Left arch is abnormal."

Bacteriological examination of his mouth failed to explain his tongue condition, and a portion of skin and subcutaneous tissue was removed for examination.

He gradually became weaker; his swallowing became more difficult. He was more tender on pressure over the pelvic area. Rhonchi and râles were heard over the lung bases, and he died on 16th February.

A post mortem and microscopical examination of tissues was made by Prof. A. C. O'Sullivan, F.T.C.D., whose reports are as follow:—

Morbid Anatomy.

The body was that of an extremely wasted man of about 50 years. There was marked colouration of the skin, which was yellow, of a brighter tinge than that seen in cases of pernicious anæmia. Post mortem lividity was present on

the back, and there was evidence of decomposition in the abdominal region. Rigor mortis had passed off. It was possible to feel innumerable subcutaneous nodules about the size of a pin's head. On section of the skin these nodules were not evident to touch and not visible. The subcutaneous fat was very scanty; it was dry and appeared to be less greasy than normal; it felt tough and fibrous. There seemed to be a change in the colour of the fat, which was darker than normal.

The Thorax.

The sternum fractured almost spontaneously when it was being manipulated after disarticulation of the sterno-clavicular joint, the manubrium was a thin shell of bone in which there was a mass of tumor, semi-transparent, in places, with dark red masses lying irregularly embedded in the soft yellowish grey matrix. The tumor was found lying all the way down the sternum, filling the marrow space and in some places expanding so that the bony shell was extremely thin; the trabeculae of bone in the cavity of the sternum had disappeared. About six of the ribs were examined, and all showed the same type of tumor. There was a large mass of tumor filling the sterno-clavicular joint.

The lungs were not adherent. In each pleural cavity there was a small collection of fluid; this was slightly blood-stained. The lungs appeared anæmic. The upper lobes were emphysematous; the lower lobes showed some superficial collapse and some evidence of œdema. The surface of both lungs gave the impression of being rough to the touch; it seemed as if there were very numerous minute hard nodules immediately beneath the visceral pleura.

The præcordial fat had atrophied, and its consistency was hard and tough. The heart was slightly enlarged. There was a complete absence of pericardial fat, and the surface felt rough, as noted in the lungs. The mitral and tricuspid valves were dilated. No other abnormalities were noted.

The Abdomen.

There was advanced post mortem change in the intestines. There was a remarkable absence of abdominal fat; the fat was hard and nodular to the touch.

The intestinal vessels were very remarkable; they were hard and very much thickened, and yet there was no evidence

of calcification. They felt like whipcord, and the lumen was very narrow.

No abnormality was noted in the intestines or stomach. The liver was smaller than normal and showed some evidence of passive congestion. The spleen was slightly enlarged, hard, and brittle. The pancreas showed no macroscopic change. The suprarenal capsules were normal. The right kidney had a tendency to horse-shoe shape; it was pale; the left kidney was normal in size and also pale. There were a few enlarged glands in the retroperitoneal tissue, and some enlarged glands were found in the mesentery.

The Neck.

The tongue was very much enlarged, extremely hard and quite inelastic. On section it was a pale yellow colour, and so tough that there was difficulty in cutting the organ. The appearance of the cut surface did not show the usual strata of muscle. It seemed as if there had been a gelatinous degeneration of the muscles, and that after degeneration the whole organ had coagulated. This is, of course, a figurative expression. The superficial muscles of the neck had also undergone this peculiar change.

A few enlarged glands were found. The thyroid gland was enlarged and firm. There was no evidence of obstruction to breathing or swallowing.

Definite projections could be felt from the inferior angle of the inferior maxilla; these did not seem to be bony.

The Bones.

Nearly all the bones examined showed masses of tumor. The clavicle, 6 ribs, the sternum, the great trochanter of the femur, and the left side of the pelvis, all showed masses of tumor where there should have been a medullary cavity. We were unable to examine other bones. We found the skull free from tumors so far as the calvarium was concerned, and the bodies of three vertebræ were roughly examined and did not reveal any tumor.

The tumor had burst through the shell of bone in one place in the left iliac bone, but had not invaded any of the surrounding tissues. There was a very large mass of tumor at the symphysis pubis. All the bones were very soft and extremely easy to break.

Histological Pathology.—The Tumor.

The tumor masses were almost entirely composed of separate cells. The stroma was extremely slight, consisting of a few delicate fibrous threads. The walls of the vessels were very thin in most cases, and the stroma in their neighbourhood was more developed, shewing as a network of homogeneous material in which the tumor cells were embedded. In a few places the vessels showed degenerated and greatly thickened walls, the degeneration having the characters of that which will be described later as existing all over the body. The tumor cells were for the most part medium-sized cells of irregular shape. The protoplasm was spongy, full of small, round, unstained spaces. The nuclei were oval or round, sharply marked off by a staining border; the chromatin of the nucleus was usually arranged in three or four masses round this border, and in the centre of the cell was a small, round nucleolus which took on acid stains, and with any stain shewed a slightly different tone from that of the chromatin. With pyronin and methyl green the chromatin stains green, the nucleolus light red and the body of the cell is a spongy network of a deeper red tint. Another type of cell, much less numerous, has one or more round very deeply staining (pyknotic) nuclei and a uniform homogeneous protoplasm which takes on a dark red with pyronin. The form of the elements of the tumor is such as has been described by several writers as a plasma cell, and this class of myeloma has been called a plasmocytoma.

The most noticeable feature in this case from the histological point of view outside the multiple bone tumors is the presence of a widespread degeneration affecting the blood vessels, both arteries and veins, and also connective tissue, especially fat tissue, and that between the bundles of muscle fibres. The substance is like amyloid in appearance, but does not give the amyloid reactions. It is present in the vessels of all parts examined, even here and there in the tumor itself. It is most marked in the vessels of the tongue, the muscles of the neck, the mesenteric vessels and in fat tissue, but it is also present in the kidney, spleen, heart, and to a less extent in the lymphatic glands. Along with this there is a form of coagulation necrosis present in the muscles of the parts affected, and in fat tissue a thicken-

ing of the capsule of the fat globule which gave a peculiar granular or gritty feel to the fat at the post mortem. It also produced the stiffening felt in the mesenteric vessels. The substance does not retain Weigert's fibrin stain, stains a faint pink with Van Geison, and generally shews little affinity for any stain.

It may for want of a better name be called a form of hyaline. The kidney shews very numerous casts filling the collecting tubes, and some of the convoluted tubes; these casts often shew differences in the staining in different parts, being with Van Geison bright yellow in the central part and brown at the periphery.

*Report by Dr. W. R. Fearon, Physiological Laboratory,
Trinity College.*

Qualitative Analysis of Urine. Summary:—

1. Reducing Sugar. Not above normal.
2. Proteins. Bence-Jones Protein present in considerable amount, together with some protein of higher coagulation temperature.
3. Blood Oxidase Reaction. Negative.
4. Diastase. Normal.
5. Indole Reaction. Slight.
6. Rothera's Reaction (acetone and aceto-acetic acid). Negative.
7. Ferric Chloride. Violet Phenolic Reaction, stable on heating. Probably due to drugs.

Hydrogen Ion Concentration. PH 6.65 by Indicator Method of Cole and Onslow.

Summary.

The remarkable features of this case, in addition to the post-mortem appearances and section reports, are:—

- (1) The association of Bence-Jones proteinuria with widespread bone-marrow trouble.
- (2) The presence of skin tumors or deposits.
- (3) The very extraordinary condition of the swollen tongue.
- (4) The progressive weakness, anemia, painful pressure.
- (5) The consistent milky appearance of the urine.

In conclusion, I thank my colleagues at the Adelaide Hospital for their kindly help, especially Dr. W. G. Harvey for his x-ray reports, and my resident, Mr. M. Bewley, who drew attention to the condition of the urine, and did the routine work, and to the workers whose reports are included in the notes.