MULTIPLE MYELOMATOSIS WITH HAEMATEMESIS AND MELAENA

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Multiple myelomatosis is a disease of protean manifestations, the diagnosis of which depends on the accurate correlation of clinical signs, symptoms, and the results of pathological and radiological investigations. Excellent general reviews of the subject are to be found in papers by Bayrd and Heck (1947), Geschickter and Copeland (1928), and Lichtenstein and Jaffe (1947) amongst others.

The disease is commonest in the male sex between the ages of 40 and 70. The main clinical features are: (a) pain, at first vague and intermittent, located in the affected bones (often most severe in the lumbar vertebrae); (b) tumour deposits in the bones, giving rise to localized swellings, pathological fractures, and deformities; (c) anaemia; (d) purpuric phenomena; and (e) "albuminuria." Radiographs of the bones often show a characteristic picture, with multiple "punched-out" areas of rarefaction.

The principal abnormalities detectable in the laboratory are hyperproteinaemia with qualitative and quantitative alterations in the plasma proteins, autohaemagglutination, the presence of Bence Jones protein in the urine, and myeloma cells in the bone marrow. These cells are sometimes present in the peripheral blood, which may show a raised serum calcium with a normal phosphate level.

The diagnosis of cases with widespread skeletal involvement is usually fairly easy, though osteitis fibrosa cystica may on occasion produce a very similar picture, especially when, as sometimes happens, the biochemical findings are equivocal. When there are no obvious bony lesions diagnostic errors are frequent, such cases being labelled "chronic nephritis," "neuralgia," "arthritis," etc.

The following cases illustrate an unusual presentation with a clinical picture suggestive of peptic ulcer.

Case 1

A man aged 62 was admitted to hospital on September 19, 1947. In the previous June he had noticed that he was losing weight and had become rather lethargic. One month later he had an epistaxis. In August he consulted his family doctor on account of increasing dyspnoea and was treated for anaemia with iron injections. Later he developed anorexia, and on September 1 vomited several times.

On admission he was seen to be pale and his skin had a faint yellowish tinge. His gums were bleeding slightly and his spleen was just palpable. His blood pressure was 90/70. The blood picture was as follows: Hb, 28%; red cells, 1,190,000; white cells 6,700 (74% neutrophils); nucleated red cells present in the peripheral blood but no myeloma cells.

A transfusion of 2 pints (1.1 litres) of Group O Rh-positive blood was given. The haemoglobin level rose by 6% and then fell. A fractional test meal was performed and blood and starch were found in all specimens. The stools contained occult blood. A tentative diagnosis of gastric ulcer or carcinoma was made and a second transfusion of 2 pints (1.1 litres) of blood was given. Gingival bleeding

continued and an ascorbic acid saturation test showed a deficient output; this was corrected by vitamin therapy.

On October 8 the patient complained of severe abdominal pain and nausea, passed a melaenaceous stool, and vomited about a pint (570 ml.) of blood-stained material. On the 9th he had another haematemesis and on the 10th his stool gave a positive reaction for occult blood. At this stage it was noted that his red cells were strongly clumped *in vitro* by his own serum, and cross-matching of blood for transfusion was hindered by massive compound rouleaux formation when donor erythrocytes were added to his serum. Despite these difficulties 5 pints (2.8 litres) of compatible blood was given by slow drip transfusion and the haemoglobin had risen to 62% by October 16. Thereafter gingival bleeding and occasional vomiting of altered blood continued and his condition gradually deteriorated. He died in coma on November 3.

Post-mortem Examination.—Only the salient features are noted. There was a pathological fracture in the body of the sternum at the junction of the upper two-thirds and lower one-third, the bone being expanded by red gelatinous material. The calvarium contained numerous dark red circular deposits of varying size, the largest being $\frac{1}{2}$ in. (1.3 cm.) in diameter, with thinning of the overlying diploë. The alimentary tract contained pin-point haemorrhages and areas of congestion, particularly conspicuous in the stomach, duodenum, and caecum. The spleen was small and soft. The myocardium was pale and flabby. The kidneys were pale and showed some reduction of their cortical tissue. There was a terminal hypostatic pneumonia. Films made from the marrow of the sternum, femur, and vertebrae showed large numbers of myeloma cells.

Case 2

A man aged 59 had been losing weight for twelve months and during this time had had occasional abdominal pain and discomfort. On January 30, 1952, he suddenly vomited altered blood and passed large quantities of dark tarry faeces, after which he felt very faint and weak. He was admitted to hospital on the following day.

On admission he was seen to be pale and shocked; his blood pressure was 90/70; haemoglobin, 34%; blood urea, 59 mg. per 100 ml.; serum potassium, 15 mg. per 100 ml. Transfusion was started and a total of 9 pints (5.1 litres) of blood was given over the next twenty-seven days, the haemoglobin rising to 63%, with great improvement in the clinical condition. The radiological appearances following a barium meal were suggestive of duodenal ulceration. By February 17 faecal tests for occult blood were negative. The patient was sent home to convalesce with a view to future surgery. A few days later he noticed that he was passing very little urine, and the little he did pass appeared to contain blood.

He was readmitted to hospital on March 20. He looked pale and ill. His face was rather puffy and there was some pharyngeal inflammation. His blood pressure was 135/70; temperature 99.4° F. (37.4° C.). A clinical diagnosis of nephritis was made. Laboratory investigations showed albumin and blood in the urine, with hyaline and granular casts in the centrifuged deposit; Hb 50%; blood urea, 73 mg. per 100 ml. The following day the patient became drowsy and anorexial. He gradually passed into a uraemic state with a brown furred tongue, his blood urea steadily rising and the haemoglobin falling. Further urine examinations revealed red blood cells in the centrifuged deposit. Transfusions were given to combat the anaemia, and on April 16, during the course of routine cross-matching and grouping, massive autohaemagglutination of his red cells was noted. On the 19th a plasma protein analysis gave the following figures: total protein 12.4 g. (albumin 2.5 g., globulin 9.9 g.). The white blood cells numbered 22,000 per c.mm. (11% myeloma cells). Platelets were scanty in the films and a count revealed 107,000 per c.mm. The patient died on April 22. The final blood investigations shortly

before death showed Hb, 36% ; urea, 448 mg. per 100 ml. ; platelets, 34,000 per c.mm. ; 20% myeloma cells in differential white blood count.

Post-mortem Examination.—The main features were as follows. The bone marrow of the skull was diffusely infiltrated by dark red gelatinous material, and a similar infiltration was found in the vertebrae and sternum. In the femoral marrow, however, the picture was different ; discrete tumour nodules were found, separated by areas of relatively normal-looking marrow. There were petechial haemorrhages in the gastric mucosa ; no ulcers were found, but the intestinal tract contained a moderate quantity of dark tarry faecal matter. The lungs showed basal bronchopneumonia. Both kidneys were large and pale. Their capsules stripped easily and the external surfaces were smooth and congested. The cut surfaces had a pale yellowish, slightly greasy appearance, and the distinction between cortex and medulla was much less clear-cut than normal. The mucosa of the bladder showed petechial haemorrhages and the left lobe of the thyroid gland contained a small colloid adenoma with areas of haemorrhage in its substance.

Histology.—Sections from the gelatinous areas in the marrow of the sternum, skull, and femur showed a diffuse and uniform replacement of the normal marrow tissues by closely packed myeloma cells. The sinusoids of the liver and spleen contained varying numbers of myeloma cells. The kidneys showed blockage of large numbers of their tubules by hyaline eosinophilic casts ; focal infiltrations of myeloma cells were present.

Discussion

These two cases of multiple myelomatosis show gastrointestinal features seldom described in the literature. Geschickter and Copeland (1928) noted nausea, vomiting, and colic in 20% of their cases, but haematemesis and melaena, in contrast to bleeding from the nose and gums, are rare. Bertoye (1904) gave a lengthy account of a case in which two attacks of haematemesis occurred, the second being fatal. Moss and Ackerman (1946) described an example of "plasma cell leukaemia" with tarry and blood-streaked stools, and they quoted a case of Askanazy's which showed haemorrhage from the gastric mucosa. Cases such as these, however, are few and far between, and the very infrequency of gastro-intestinal haemorrhage in myelomatosis may easily lead the clinician to make an erroneous diagnosis of peptic ulcer or gastric neoplasm. The correct diagnosis may be made in the laboratory, and the patient may be spared an unnecessary operation, if certain clues previously indicated are followed up.

Of these, the ones most likely to be detected initially are the phenomena of autohaemagglutination and massive rouleaux formation, which may give rise to great difficulties in cross-matching blood for transfusion and in performing blood counts, particularly when Hayem's diluent is used for red-cell estimations. Rouleaux formation was found by Bayrd and Heck (1947) in 60% of their cases, and, in common with other authors, they noted that it was correlated with a raised serum globulin level and an increased erythrocyte sedimentation rate. "Streakiness" of blood films may also be noted in such circumstances. With regard to the sedimentation rate a peculiar discrepancy between the results obtained by the Wintrobe and Westergren techniques is apparent in some cases, as the former may give figures within the normal range when the Westergren result is 100 mm. in one hour, or even higher.

The finding of any of these haematological abnormalities should suggest the possibility of myelomatosis, and further investigations should be made. From the practical standpoint the next most useful procedure is the estimation of the plasma proteins. In this laboratory the copper sulphate specific gravity technique is used as a rough preliminary test. Hyperproteinaemia, with reversal of the albumin/globulin ratio, is often found. Bayrd and Heck (1947)

found it in 73% of cases and Gutman and Gutman (1936) in 35 out of 57 cases. Sometimes only the globulin fraction is increased, the total protein content of the plasma being within normal limits. Recent work by MacLagan *et al.* (1952) indicates that such alterations in the plasma protein pattern lead, apparently in a definite sequence, to abnormal results being obtained from various liver-function tests. The total serum globulin and the albumin/globulin ratio are first to be affected, followed by the ammonium sulphate turbidity, zinc sulphate turbidity, serum colloidal gold, and thymol turbidity and flocculation reactions, in that order.

Examination of the urine for Bence Jones "protein" should, of course, be carried out, but it must be appreciated that it may be present only intermittently. Technical difficulties are sometimes encountered, especially when the urine contains only small amounts of the substance, or when large quantities of ordinary albumin are also present. Discombe *et al.* (1937) have described reliable methods for overcoming these difficulties.

Myeloma cells may be detected in the peripheral blood, though the frequency with which they are found is rather variable. Lichtenstein and Jaffe (1947) found 2 out of 35 cases, and Morissette and Watkins (1942) 41 out of 56 cases. Except in the rare "plasma cell leukaemia," their presence in the peripheral blood tends to be a late, or terminal, phenomenon. Bone-marrow biopsy will enable a conclusive diagnosis to be made if a myelomatous area can be located.

With regard to the cytological features, several authors have described variations in the myeloma cells ; thus it is commonly recognized that there is a "small-cell" type, in which the tumour cells resemble plasma cells, and a "large-celled" type, in which the cells have large, pale, round, oval, or reniform nuclei showing fine chromatin stippling. There may be rod-shaped bodies of variable staining and vacuoles in the cytoplasm. The distinctive features of myeloma cells are best demonstrated by special staining techniques, such as the Unna-Pappenheim method.

In conclusion, it should be mentioned again that in some cases of myelomatosis an erroneous diagnosis of "nephritis" may be made, as happened initially in Case 2 above, during his second admission to hospital. Though the only direct effect of myelomatosis on the kidney seems to be the deposition of proteinaceous casts in the tubules (Bell, 1933) the clinical picture is not uncommonly complicated by coexisting arteriosclerosis or pyelonephritis. Usually, however, the correct diagnosis can be made by performing the cardinal laboratory investigations outlined above.

Summary

Two cases of multiple myelomatosis, with haematemesis and melaena, are recorded. The main laboratory investigations necessary for the diagnosis of the disease are outlined.

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