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Bone Marrow Embolism in Multiple Myeloma*

ROMAN KNOBLICH and EUGEN KREINER
Department of Pathology, Hurley Hospital, Flint, Michigan

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Knochenmarksembolie von multiplem Myelom

Zusammenfassung. Knochenmarksembolie im Krankheitsverlauf von multiplem Myelom wurde bisher noch nicht in der Literatur beschrieben. In 6 von 14 Patienten mit multiplem Myelom, die von 1952—1967 im Hurley Hospital zur Sektion kamen, wurden Emboli in den kleineren Ästen der Lungenschlagader festgestellt. In 4 Fällen waren diese Emboli ganz eindeutig als Knochenmark zu erkennen. In 2 weiteren Fällen konnten Emboli vermutet werden. Die Erkennung von Knochenmarksembolien im histologischen Präparat kann durch drei Umstände erschwert oder sogar verhindert werden: die in der Regel sehr geringe Zahl solcher Emboli, die bald einsetzende Degeneration und Auflösung und schließlich die Herkunft aus pathologischem Mark. Letzteres weist besonders starke Veränderungen bei Patienten auf, die mit Bestrahlungen oder Chemotherapeutica behandelt wurden. Meist sind diese Knochenmarksemboli lediglich Zufallsbefunde bei Sektionen. Wir meinen jedoch, daß sie gelegentlich auch klinisch in Erscheinung treten können. In einem unserer Fälle führte massive Embolisation von Knochenmark innerhalb kurzer Zeit zum Tod.

Summary. Multiple myeloma and the accompanying osteolytic process frequently lead to recognized or subclinical fractures. As a consequence of these fractures bone marrow embolism may occur. During a 15 years period fourteen patients with myeloma were autopsied in Hurley Hospital. In four of the fourteen autopsies unequivocal bone marrow embolism and in two autopsies possible bone marrow embolism was found. In one of the patients the bone marrow emboli, together with fat emboli, were the cause of death. In the other three cases the emboli were incidental findings. We suspect that bone marrow embolism may be a rather frequent complication of myeloma and may lead to pulmonary complications. Occasionally it may be the cause of death.

Bone marrow embolism of pulmonary blood vessels was first described by LUBARSCH in 1898. It is due to a disruption of bone marrow and the consequent escape of marrow particles into the venous circulation. The disruption of the bone marrow may be caused by violent trauma resulting in obvious multiple fractures of cortical and medullary bone as seen in battle casualties (WARREN, 1946) and in aircraft and automobile accidents (MASON, 1959; RAPPAPORT, 1951); it may also be caused by minimal trauma resulting in single insignificant fractures accompanying diagnostic sternal marrow puncture (YOELL, 1959), or external cardiac massage (WINKEL, 1961; GARVEY, 1964; SILBERBERG, 1964) or following a thoracotomy involving rib resection (MCKEOWN, 1955) or sternal transection (SCHMIDT, 1958). In these conditions cortical and medullary bone is fractured and these fractures are clinically and roentgenologically detectable. Bone marrow embolism, however, can also occur when trauma produces "medullary fractures"

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without clinically or roentgenologically detectable cortical fractures. This phenomenon has been described as a rarity in a variety of conditions such as eclampsia, tetanus, shock therapy and epilepsy (LUBARSCH, 1898; RAPPAPORT, 1951). To our knowledge the occurrence of bone marrow embolism in cases of multiple myeloma has not been described in the medical literature. A clinicopathologic study of 14 cases of multiple myeloma constitutes the basis of this report.

Material and Methods

The Hurley Hospital autopsy material between 1952 and 1967 includes 14 cases of multiple myeloma. The patients ages ranged from 50 to 84 years. Eight were men and 6 were women. Eight patients had bone marrow aspiration in this institution and 6 also showed an electrophoretic protein pattern consistent with myeloma. There was some degree of generalized involvement of the skeletal system in 12 cases; in the two remaining cases the myeloma was discovered incidentally at the time of autopsy in the form of a single tumour of a vertebral body, (in these 2 cases it was impossible to exclude generalized myeloma from the available clinical records and from the routine autopsy material). In all 14 cases the available microscopic material was reviewed. In 11 cases wet tissue was available from which frozen sections were prepared and stained for fat with Sudan IV. X-ray films were reviewed in 10 cases.

Report of Cases

Case No. 1. An 84-years-old white man had a histologically proven bronchogenic epidermoid carcinoma of the upper lobe of the left lung. A bone marrow aspirate six months prior to death established a diagnosis of myeloma. The roentgenologic examination revealed multiple osteolytic lesions of the long bones. The cause of death was intracerebral hemorrhage. Numerous blocks of lung tissue were examined. Only one section revealed the presence of a bone marrow embolus.

Case No. 2. In a 59-years-old white woman the diagnosis of multiple myeloma was established $4^1/_2$ years prior to death in marrow aspirates and by protein electrophoresis. Roentgenologic examination showed multiple osteolytic lesions of bones and also fractures of ribs, vertebrae and long bones. The patient died quite suddenly. No obvious cause of death was established upon macroscopic examination of the body. Microscopic examination revealed extensive bone marrow and fat embolism in numerous sections of lung tissue (Fig. 1). Some of the emboli showed early organization (Fig. 2). The cause of death was extensive marrow and fat embolism of the pulmonary vascular tree.

Case No. 3. In a 62-years-old white woman the diagnosis of multiple myeloma was established in bone marrow aspirate and by protein electrophoresis. At autopsy involvement of sternum, ribs, clavicles and vertebrae by multiple myeloma was found. Numerous lung sections were examined; bone marrow emboli could be demonstrated in only two of the sections. There was no associated fat embolism. In one section a classical bone marrow embolus made up of fat, hematopoietic elements and supporting marrow framework was found in a blood vessel. Other blood vessels in the vicinity were occluded by disintegrating emboli without fat elements (Fig. 3). The cause of death was congestive heart failure.

Case No. 4. A 65-years-old white man was found to have multiple myeloma. He received x-ray therapy and chemotherapy intermittently. He died 6 years after the diagnosis was made. Prior to death roentgenologic examination showed widespread involvement of the skeleton by multiple myeloma; there were numerous fractures. At autopsy bone marrow embolism was suspected when a small but macroscopically visible embolus was found in a small branch of one of the pulmonary arteries. The embolic material was impressed on a glass slide and stained by the Wright technique. The preparation showed hematopoietic and fibroblastic elements. In several sections of lung tissue marrow emboli consisting of hematopoietic and fibroblastic elements were found (Fig. 4). One of the emboli contained a well-preserved megakaryocyte. Emboli containing fat cells were not found. There were several old, organized emboli in the smaller pulmonary vessels. Sections from various marrow-containing bones showed myelofibrosis and infiltration with myeloma. The appearance of the bone marrow

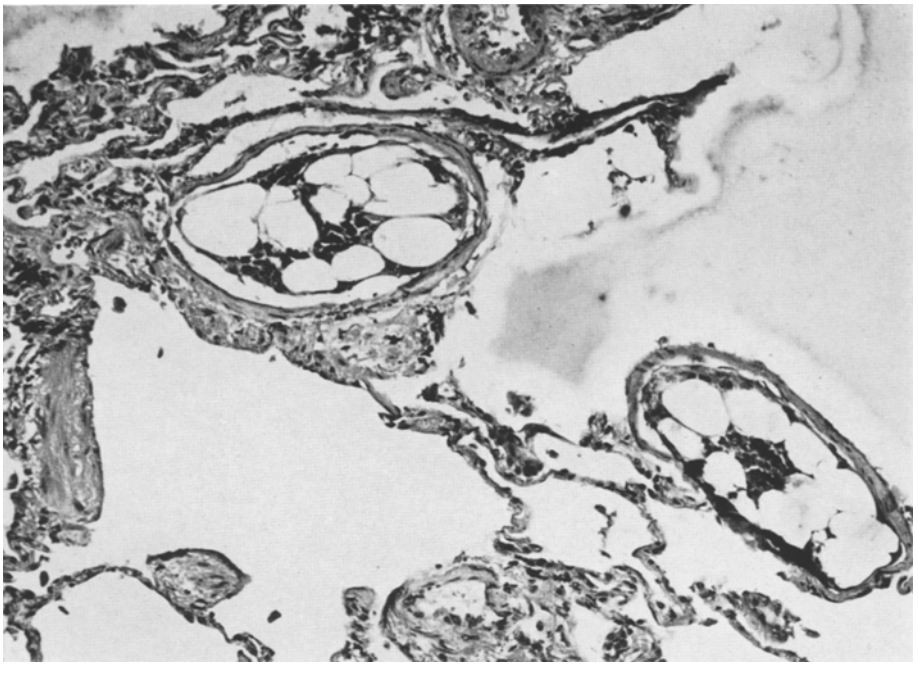

Fig. 1. Bone marrow emboli in two adjacent arteries. The emboli contain both fat cells and hematopoietic cells. H.E. × 100

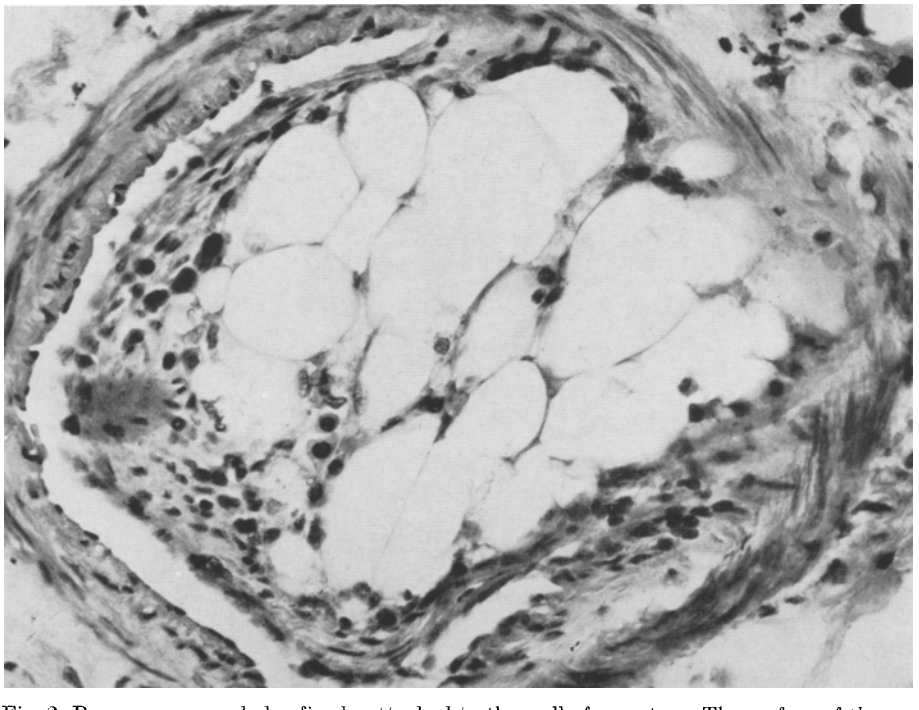

Fig. 2. Bone marrow embolus firmly attached to the wall of an artery. The surface of the embolus has become covered by endothelium. The marrow contains myeloma cells. H.E. × 450

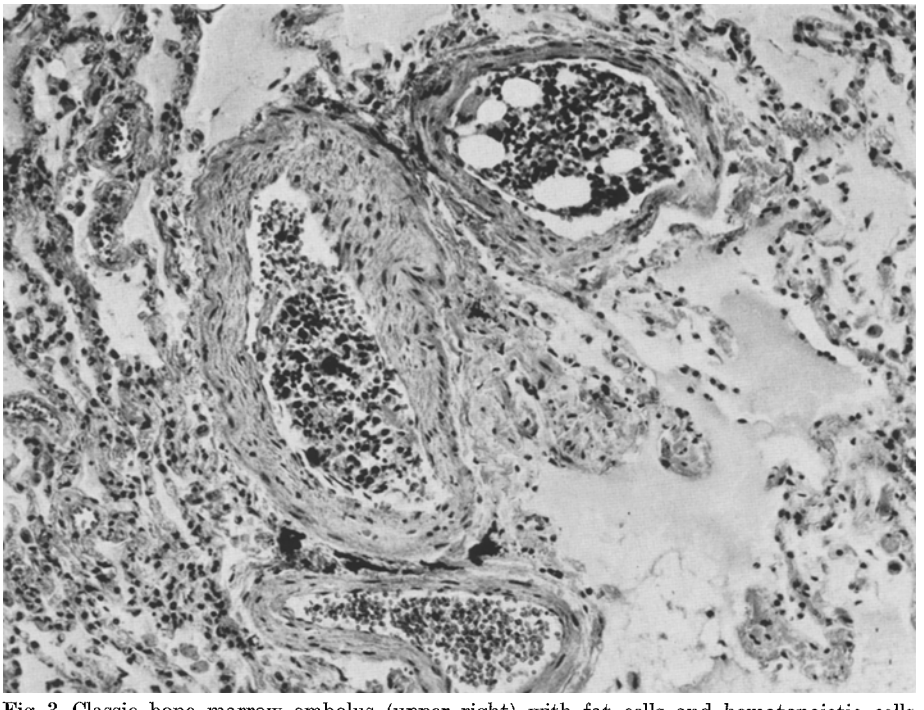

Fig. 3. Classic bone marrow embolus (upper right) with fat cells and hematopoietic cells. A disintegrating embolus is also seen (center). H.E. × 100

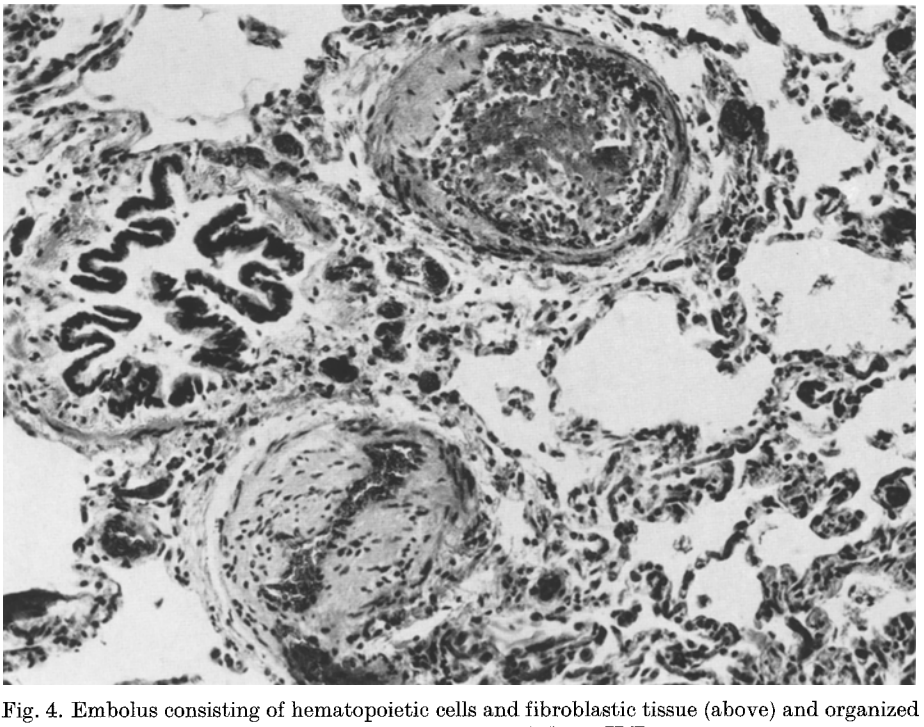

Fig. 4. Embolus consisting of hematopoietic cells and fibroblastic tissue (above) and organized embolus showing recanalization (below). H.E. × 100

in the sections was similar to that of the marrow particles in the pulmonary vessels. The cause of death was bronchopneumonia.

Case No. 5. A 62-years-old Negro woman suffered from multiple myeloma complicated by amyloidosis of the heart and kidneys. A clinical diagnosis of multiple myeloma had been confirmed by bone marrow aspiration and protein electrophoresis. The autopsy revealed diffuse involvement of the skeleton by multiple myeloma. Microscopic examination showed organized emboli in the lumen of the smaller branches of the pulmonary arteries. Clusters of cells closely resembling marrow elements were found in the organizing emboli. The cause of death was renal failure due to amyloidosis of the kidneys secondary to multiple myeloma.

Case No. 6. A 63-years-old white woman presented with a compression fracture of the 9th thoracic vertebra. At autopsy a solitary myeloma was found in the fractured vertebra. Microscopic examination showed organizing emboli in the smaller pulmonary blood vessels. The emboli contained cells resembling those in the fractured vertebra. The cause of death was cerebral hemorrhage.

Discussion

In plasma cell myeloma there is osteolysis of the medullary bone spicules and of the cortical bone. Disruption of marrow elements will occur when the cortical bone (and consequently the medullary bone) fractures; it may also occur without cortical fractures. In most cases of multiple myeloma fractures of cortical or medullary bone occur during the course of the disease and therefore one should not be surprised to find bone marrow embolism of the pulmonary vascular tree. In our series of 14 cases of multiple myeloma there were pulmonary emboli in 6, and in 4 of these the emboli were composed indisputably of bone marrow. In an additional 2 cases the findings suggested strongly that the emboli were formed of bone marrow. Most likely we should have found an even higher incidence of bone marrow embolism if more tissue had been available for microscopic examination. As LUBARSCH pointed out, bone marrow emboli are not very numerous in most of the cases in which they are found and so they can easily be missed in routine autopsies. In 2 out of 3 cases which we autopsied after we had become aware of the phenomenon of bone marrow embolism in multiple myeloma, we found bone marrow emboli; in one case only a single embolus was seen in 12 blocks of lung tissue examined.

The true incidence of bone marrow embolism following trauma is hard to evaluate as it seems to depend upon the severity of the trauma and upon the number of bones fractured and also upon the diligence with which emboli are looked for (SEVITT, 1962). Published estimates of the incidence of bone marrow embolism following trauma range from 3% (WARREN, 1946) to 40% (MASON, 1959). The search for bone marrow emboli in pulmonary arteries is complicated by the fact that bone marrow particles in the pulmonary blood vessels have a tendency to disintegrate and to disappear or become organized. Success in detecting bone marrow emboli will therefore depend upon the survival time following cortical or medullary fracture (MASON, 1959). A short survival limits the opportunity for disruption of the fragments in the pulmonary vasculature and they are then recognizable in sections; longer survival allows more time for disruption to occur. The nature of the emboli in cases of bone marrow embolism following fracture of bones containing normal marrow is easily recognizable. Bone marrow emboli in cases of multiple myeloma may not show the classic histologic picture of bone spicules, fat cells and hematopoietic cells but will frequently consist of plasma cells with few or no bony spicules and no fat cells. Fractures in multiple

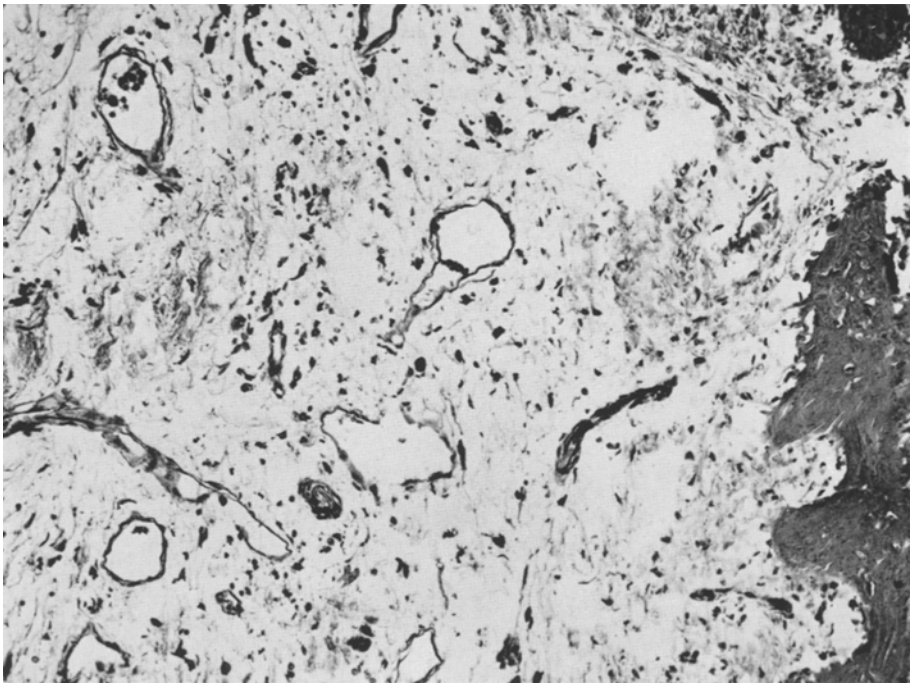

Fig. 5. Bone marrow showing marked degree of myelofibrosis (case 4). The patient had been treated with x-rays and chemotherapeutic agents for many years. H.E. × 100

myeloma may involve bones that as a result of chemotherapy of the tumour contain a fibro-fatty or fibrous bone marrow (Fig. 5): emboli from such areas may be overlooked or may not be recognized as marrow.

If bone marrow embolism is very massive it can be fatal. In most of our cases in which bone marrow embolism occurred, the bone marrow particles in the pulmonary vascular tree may have been a contributory cause of death but were not thought to be solely responsible. Occasionally, bone marrow embolism complicating myeloma can be the sole cause of death, as in case 2. In this case the gross autopsy examination did not reveal an obvious cause of death and this led to consideration of the possibility of marrow embolism. The microscopic examination substantiated this when bone marrow and fat emboli were found in substantial quantities. The facts that in most cases bone marrow emboli do not produce death and that it is occasionally possible to demonstrate old organized emboli in the presence of fresh emboli suggest that during the natural course of myeloma non-fatal bone marrow embolism repeatedly occurs. Repeated bouts of respiratory disturbance, especially pneumonia, are well known to occur as complications in the course of myelomatosis and are usually thought to be due to the altered immunoglobulin state occurring in that disease (ZINNEMAN, 1954). Whether repeated bone marrow embolism during the course of multiple myeloma might cause or precipitate some of the respiratory difficulties has not been determined by our anatomic studies.

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Dr. ROMAN KNOBLICH
Department of Pathology
Hurley Hospital
Flint 2, Michigan 48502, U.S.A.