症　　例

Multiple Myeloma

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Since the classic description of "mollitis ossium" by DALRYMPLE (1846), BENCE JONES (1848) and MACINTYRE (1850) appeared, much studies about controversial multiple myeloma have been reported. The exact nature of this disease and the true origin of the predominant cell of this tumor have not been established with definitness. In Japan KURE et al. described the first one case in 1915. Recently numerous articles have been written on the subject which ascribed to the improvment of the diagnostic procedure, particularly advancement of biochemical aberrations relating to the blood serum.

From the statistic point of view, HINO presented 305 cases until February, 1960 and on the other hand IMAMURA and his associates investigated the incidence of myeloma in Japan, that is, 377 cases until October, 1960, and otherwise 64 out of 3771 cases of bone neoplasm have been collected by the Central Japan Orthopaedic and Traumatic Surgical Society till April, 1963 (Central Japan included Tokai-Hokuriku, Kinki, Chugoku and Shikoku district).

Here is our report on three cases of multiple myeloma. All cases died and autopsy was performed one of them.

CASE REPORT

Case 1. (Table 1 & 2, Fig. 1-4, 8 & 12)

This is a 68 year old, male who complained of dull and intermittent severe pain on the right forearm since 3 or 4 months prior to admission. One month prior to admission, he falled down the floor with extended right arm and went to a dispensary. An X-ray examination, at that time, revealed a fracture of the right radius. And then he was refered to our out-clinic on January 23, 1962.

The painfull swelling was predominant on the anterior aspect of the right forearm and accompanied with disturbance of the movement. The roentgenogram appeared pathologic fracture of the right radius on the mid portion with lytic rarefaction of the medulla which supposed to be a bone tumor. Both fragments of the radius were not particularly dislocated.

On the admission date, operation is carried out. The mid portion of the right radius

Table 1 Laboratory Data

	Case 1	Case 2	Case 3
BLOOD			
R. B. C. (per cu. mm.)	3920000	1700000	2670000
Hb. (Gm/dl)	12.3	4.8	8.2
Ht. (%)		12	20
W. B. C. (per cu. mm.)	8300	9200	3500
Basophils (%)	2.0	—	1.0
Eosinophils (%)	—	1.0	—
Neut. (%) Juvenile	—	—	1.0
Neut. (%) Nonfilament	2.5	7.5	12.0
Neut. (%) Filament	67.0	73.5	43.0
Lymphocytes (%)	25.0	10.5	42.0
Monocytes (%)	3.5	7.5	1.0
Plasma cells (%)	—	—	—
Sedimentation rate (Westergren)			
in 1st hr. (mm.)	132	176	175
in 2nd hr. (mm.)	140	176	176
SERUM			
NPN (mg/dl)		77	27
Ca (mEq/l)	5.0	6.1	5.0
P (mg/dl)	3.2	5.0	4.6
Fe (γ/dl)		112	
Cu (γ/dl)		160	
Uric acid (mg/dl)	5.4	6.8	5.4
Alkaline P-ase (Bodansky unit)	8.46	14.4	1.98
Total proteins (Gm/dl)	8.8	10.4	13.8
ELECTROPHORETIC FRACTIONS OF SERUM PROTEINS			
Albumin (%)	29.4	23.2	24.2
α-Globulins (%)	7.2	5.4	7.2
β-Globulins (%)	8.6	3.5	9.0
γ-Globulins (%)	54.8	67.9	59.6
A/G	0.42	0.30	0.32
BONE MARROW PICTURE			
No. of nucleated cells (per cu. mm.)	166000	100000	35000
Myeloblaste (%)	0.8	—	0.8
Promyelocytes (%) Neut.	1.4	1.2	2.6
Promyelocytes (%) Eosin.	1.2	—	0.2
Myelocytes (%) Neut.	16.2	1.0	8.2
Myelocytes (%) Eosin.	1.2	0.2	—
Metamyelocytes (%) Neut.	13.8	3.2	8.6
Metamyelocytes (%) Eosin.	0.8	—	—

Nonfilament (%) Neut.	9.0	0.8	11.6
Nonfilament (%) Eosin.	0.2	—	—
Filament (%) Neut.	11.4	1.8	5.8
Filament (%) Eosin.	1.8	—	0.8
Lymphocytes (%)	10.8	2.2	18.6
Monocytes (%)	3.4	2.2	6.0
Plasma cells (%)	4.6	84.4	10.8
Reticulum cells (%)	2.4	1.2	1.0
Erythroblaste (%) Basophil.	3.8	0.4	6.2
Erythroblaste (%) Polychrom.	10.4	0.6	7.6
Erythroblaste (%) Orthochrom.	6.8	0.8	11.2
URINE			
Specific gravity	1022	1013	1014
Reaction to litmus	slightly acid	neutral	slightly acid
Albumin			
Sulfosalicylic acid test	(++)	(++)	(++)
Heat and acid test	(+)	(+)	(++)
Esbach's quantative method		1.8‰	
Bence Jones' protein	(−)	(−)	(−)
Sediment Erythrocytes	(++)	(−)	(++)
Sediment Leucocytes	(+)	(+)	(−)
Sediment Epithels	(−)	(−)	(−)
Sediment Casts	(−)	(−)	(−)
LIVER FUNCTION			
Takata's reaction	(+++++)	(++++)	(+++++)
Co. R.	8 (9)	0 (1)	9
Cd. R.	8	18 (20)	4
Icterus index (units)	3	2	2
B. S. P. test (30 min.)		5%	
RENAL FUNCTION			

Renal clearance	P.S.P. test
R.P.F. 334cc/min.	5 min. 5%
R.B.F. 393cc/min.	60 min. 25%
G.F.R. 56cc/min.	120 min. 35%
F.F. 0.167	

exposed with thin periosteum and cortex. Around the fracture site, small amount of hemorrhage is revealed. The medulla is repleted with grayish granulation which noted cartilage consistency. There are some hard masses surrounding soft tissue. The complete curettage of the tumor can not be done. Therefore, tumor with cortex and superimposed one of the muscle origin are together resected. And about 6.5cm length of bone defect takes place. An inlay graft, triangle pillar $7.5 \times 0.5 \times 0.7$cm in length is transmitted from the right tibia.

Chemotherapy and Predonin are given. Gradually, cough and sputum with right chest pain had been increased. Sometimes intermittent fever was remarkable. Despite of complaining of headache day by day, the patient returned home on March 1, 1962.

Table 2 The Distribution of the Bone Lesions

	Case 1	Case 2	Case 3	IMAMURA (1962)
Skull	(+)	(−)	(+)	149 (71.9%)
Ribs	(+)	(−)	(+)	140 (70.4%)
Vertebra	(+)	(+)	(+)	135 (67.9%)
Pelvis	(+)	(−)	(+)	107 (53.8%)
Femur	(+)	(−)	(+)	79 (39.8%)
Humerus	(+)	(−)	(+)	69 (34.5%)
Clavicula	(+)	(−)	(+)	53 (26.7%)
Sternum				47 (23.6%)
Tibia	(+)	(−)		24 (12.1%)
Fibula	(+)	(−)		
Scapula	(−)	(−)		24 (12.1%)
Radius	(+)	(+)		21 (10.6%)
Ulna	(+)	(−)		
Bone of Face	(−)	(−)		15 (7.5%)
Bone of Hand	(−)	(−)		1 (0.5%)
Bone of Foot	(+)			

Note : (+) shows bone lesions revealed by x-ray.

IMAMURA et al. summarized 199 cases of bone lesions.

He was re-admitted on May 31, 1962 with increased severe pain in the lumbar region and both thighs, accompanying with painless swelling on the parietal portion of the head. The painfull localized swellings in the chest or lower extremities were particularly increased and general condition was slowly deteriorated with participation of dental hemorrhage. Therefore, daily blood transfusions were performed. His condition had become poor with diastolic cardiac murmur, decreased frequency of respiration, dullness on the right lung field and high fever. He died on September 22, 1962. During the 2nd admission, sedativa, chemotherapy as well as Tespamin or Toyomycin, Durabolin and Predonin were employed.

Postmortem record (Fig. 9-11 & 13-20)

The body is that of a well developed, emaciated male. The skin has poor elasticity, fine texture, pale in color. Two operation scars are present of different sizes. One of them is on the anterior aspect of the right lower leg and another on the anterior aspect of the right forearm. The subcutaneous tissue is scant and shows normal distribution. Several palpable masses are present on the parietal portion of the head, the right side of the thorax, the knee and anterior aspect of the left leg which have soft elasticity and no remarkable fluctuation is present. Abnormal venous dilatation is seen on the abdomen. The distribution of body hair is average. On the other hand, the eyes, the nose, the mouth and the tongue have no particular pathologic changes.

Chest : The chest is symmetrical. Several white yellowish masses of been- to walnut size considered probably metastatic foci are seen in the intercostal muscles, the ribs, the cartilage and the diaphragm. The mediastinal lymph nodes are anthracotic and enlarged, especially on the right hilar nodes which microscopic examination shows plasma cell in-

filtration.

Left lung : The entire surface is smooth and not seen any adhesions. The mediastinal aspect of the base is respectably adherent to the pericardial sac and the diaphragm. The posterior surface reveals a dark gray parenchyma. The main bronchus is patent. Multiple sections reveal slightly brochiectasis and increased interstitial fibrosis. Microscopic examination shows increased fibrotic tissue around alveoli with epithelioid and lymphocytic reaction. Some alveoli are filled out by homogenous mucus.

Right lung : The organ is markedly shrunken with increased densities. The anterior aspect is covered by slightly thickned pleura and mediastinal aspect of the base is not adhered. Multiple sections reveal bronchiectasis and slightly increase of interstitial fibrosis with enlarged hilar nodes. This collape of the right lung might be a transplantation of metastatic tumor in the hilar nodes. Microscopic examination reveals pulmonary fibrosis with numerous plasma cell infiltration. And no epithelioid cell reaction is appreciable.

Heart : The heart is enlarged. It weighs 450 Gms. The pericardial sac contains about 130 cc of yellowish clear fluid. The pericardium shows a pale color and has a normal amount of fatty tissue. In some area of the epicardium a few of white yellowish tumor foci is present and not adhesive. The interventricular septum reveals no pathologic findings. The left ventricular myocardium has a normal thickness but a questionable tumor lesion is present on the anterior upper aspect. The right ventricular myocardium has an average thickness and shows no remarkable findings. Mural thrombosis is absent. The valves are not calcified. The coronary arteries are well patent without sclerotic changes of their intima and normal in distribution. Microscopic examination of the left ventricle reveals metastatic foci from the epicardial tissue which is filled out by myeloma cells. And the right ventricle shows normal myocardium with mild fatty infiltration in the epicardium.

Abdomen : General anatomy of organs of abdominal cavity and their relationship of localisation are normal with content about 3100 cc of yellowish grayish fluid.

Liver : The liver is atrophic and weighs 820 Gms. The external surface is smooth and shows no adhesions to the diaphragm. The cut section has a general yellowish pale brown color. The structural markings are discernible. Lobular architecture is preserved in microscopic findings with increased polymorph nuclear leucocytes in sinusoids.

Billiary passages and hepatic vessels are patent.

Spleen : The spleen is not enlarged. It weighs 70 Gms. The external surface glisters and shows no adhesions. Cut section reveals a general reddish-brown color and flabby in consistency. The trabeculation and Malpighian bodies are slightly observed.

G. I. tract : The esophagus has no ulcerations or varicosities. The stomach contains about 330 cc of undigested yellowish food. It shows no ulcerations. There are no abnormalities of the duodenum, the small intestine, the appendix and the large intestine. Microscopic examination shows no remarkable findings in G. I. tract.

Kidney : Both kidneys together weigh 360 Gms. They are of equal size. The capsule can be striped with ease. The external surface is smooth and pale brownish in color with scant fatty tissue. The cortex of both kidney is normal in width. The right kidney has a stone of bean size in the upper pole of the medulla and the pelves are slightly dilated with no congestion. Microscopic examination reveales tubules and interstitial tissue

infiltrated with polymorphnuclear leucocytes and round cells. Some collecting tubules filled out with colloid casts. And the nests of glomeruli are normal but a few of them shows hyaline degeneration. There are no remarkable pathologic changes in the ureters, the bladder, the adrenals and the prostate.

Skeleton : There are some yellowish tumors in the long bones and the body of the vertebrae which microscopic examination shows plasma cell infiltration with small dark eccentric nuclei.

Pathologic diagnosis as follows :

1. Plasma cell myeloma.
2. Extraskeletal myelomatous infiltrations in the right lung, the hilar nodes, the left ventricle, the ribs, the costal cartilage, the intercostal muscles and the diaphragm.
3. Collaps of the right lung with exudative pleursy.
4. Bilateral pulmonary edema and slight bronchiectasis.
5. Bilateral pyelonephritis with right nephrolithiasis.
6. Ascites, mild.

Case 2. (Table 1 & 2, Fig. 5 & 21.)

A 68 years old male suffers from lumbar pain one month ago. The pain is transmitted to the left side of the abdomen. He attends to our out-clinc on September 5, 1961. At that time an X-ray examination appeared mild osteoporosis with osteophytes in the lumbar vertebrae with slight stiffness. Durabolin 25 mgs are employed once a week with continuance for 5 months. On the other hand, OTC (Orthopaedic therapeutic corrective) support is administrated. His condition had become in satisfactory. On December 11, 1961 he is admitted to the Department of Internal Medicine in our hospital with chief complaining of anemia and albuminuria. December 24, 1961, the marrow punctures are performed and from the several laboratory data multiple myeloma is diagnosed. Since January 11, 1962 blood transfusions are employed. His general condition is good. Sometimes he is suffered from lumbar pain and right intercostal pain. No cardiac murmur and no abnormal respiration are seen. On May 21, 1962 slight dental hemorrhage is noted and one week after he is discharged. During he is in our hospital, Durabolin, Predonin and anti-anemic drugs are given. After he returned home his condition has been satisfactory for a while, however he died three months after.

Case 3. (Table 1 & 2, Fig 6, & 22)

This 64 year old, male had long history of anemic condition. He had suffered from severe grade of diarrhea without any weight loss or loss of appetite for 3 or 5 months after the 2nd World War. The disturbance of the liver and anemia were diagnosed in 1948. Such condition had been under control and appeared in good health until April, 1960. However, anemia was again pointed out on June, 1960 and admitted to a certain hospital and treated till the end of December, 1960. Multiple myeloma was diagnosed by marrow puncture smear on November, 1960. Thereafter he attended to our out-clinc with complaining of lumbar and chest pain with the limitation of trunk movement on May 22, 1963. At that time, the skull had no tenderness but stiffness of the lumbar region was characteristic.

Patient was admitted to our hospital on June 4, 1963. Continuous pain in both side

of the chest with intermittent cough were noted, but no remarkable fever. Since August 10, 1963 he had been able to sit down on the bed and his general condition had been appeared to be improved by Predonin or anabolic steroids.

However, swelling of his face accompanying with both side of hyperemic conjunctivitis had been observed. Marrow puncture was done on September 10, 1963. Localized swelling of the right ribs had been acknowledged, since September 19, 1963 and chemotherapy as yet had been continued. He expired on October 16, 1963.

DISCUSSION

Multiple myeloma is often described as a term of plasma cell myeloma. It should be regarded as a neoplastic disease which occupies a place between frank tumors and leukemias. CARSON and his associates grouped 90 patients into three categories: (1) the multiple or diffuse group, (2) those with an apparent solitary bone lesion, (3) those with primary extramedullary tumor. Recently IMAMURA et al. grouped 246 myeloma into five types in Japan, which types could be shifted each other (Table 3). According to their classification, our cases belong to multiple myeloma (Case 1 and 3) and diffuse form (Case 2). Setting aside of the comprehensive description of this disease, a few of interesting points in our cases are presented in this paper.

Table 3 Classification of Plasmocytoma (IMAMURA et al.)

A) Medullary Plasmocytoma		
1) Plasma Cell Leukemia	} Myeloma (in a narrow sense)	} Myeloma (in a wide sense)
2) Diffuse or Generalized Myeloma		
3) Multiple Myeloma		
4) Solitary Myeloma		
B) Extramedullary Plasmocytoma		

(I) As regards the problems of pathologic fractures detected by roentogenologic examination, RITVO described that the incidence of fracture were frequent and that of pathologic fracture might be high. CARSON and his co-workers pointed out that pathologic fractures were mostly involved the vertebral column, the ribs, the pelvis and the sternum in over half of the cases. Only 4 out of 46 cases of pathologic fractures were revealed in the long bones as so femur and humerus. IMAMURA et al. described that the incidence of pathologic fracture of the long bones appeared 7 out of 253 cases, that is, 2.8% in Japan. YOSHIOKA et al. anounced that the frequency of pathologic fracture of multiple myeloma as twice as metastasis of carcinoma.

Case 1 was noted pathologic fracture of the right radius which was a main intial symptom at the time of admission. It might be very rare finding that pathologic fracture of the long bones appears intially. On the other hand, pathologic fracture does not always produce symptoms, as showing in case 3 (Fig. 7) the left ischiadic bone had no pain of this region during his illness.

(II) Upon the pathologic findings, extraskeletal myelomatous infiltration, LICHTENSTEIN

presented in two cases of his autopsy material. One was in the liver and another in the lymph nodes. According to his literature, involved organs are reported as follows: the lung (MALLORY and others), the heart (PINEY et al. and others), the pancreas (PINEY et al. and others), the kidney (CARLISLE and others), the adrenal gland (PINEY et al.), the tonsil (JACHSON and others), the male gonad (ULRICH) and the skin (DUVOIR et al. and others).

Case 1 presented visceral involvements in the heart, the right lung, the hilar lymph nodes, the intercostal muscles and the diaphragm.

These involvements of myeloma were not considered as "extramedullary plasma cell tumor" reported by CONNER and others. This tumor is primarily originated from the visceral organs such as the upper respiratory tract, the oral cavity, the kidney, the ovary, and the intestine. Case 1 has no lesions in these organs but predominant myelomatous infiltrations in bone marrow.

(III) As to the duration of symptoms from the time of establishment of diagnosis, CARSON et al. described that thirty one (52 per cent) out of 60 patients with multiple bone involvements died within 3 months since the time definitely diagnosed. Twenty two (36 per cent) lived for 3 to 24 months and only 3 lived longer than 24 months. LICHTENSTEIN reported that the average period of survival following the onset of symptoms was about 2 years, although occasional patients were alive along as 10 years or more. Concerning to the period of survival from the onset of symptoms in Japan and overseas by IMAMURA et al. reported that mean value is 13 to 15 months (average 20 to 30 months) in Europe and United States, on the other hand, in Japan mean value 9.6 months (average 14.2 months), Such less the period of survival in Japan might be due to the more high incidence in diffuse type. HINO anounced that a half of his 55 cases died within one year and a case was living more than two years.

Our case of No. 3 has been living for 3 years from accurately diagnosed, it will be rare case in Japan.

(IV) The therapy of multiple myeloma is directed to be beneficial, but usually not to be curative. Roentogen therapy and drugs including chemotherapy are more common. WAKAMATSU and his associates reported that under the hypothesis of similarity of bone states in osteoporosis and in multiple myeloma, 821 million units of estrogen were administrated and healing appeared in the affected bones though any histological proliferation of bone structures did not happened in multiple myelama. In spite of the mechanism of pain in multiple myeloma is not clearly acknowleged, but anabolic steroid hormons are usually employed to reduce the pain of malignant metastatic bone tumors as H. H., one of the authors had already reported. On the other hand, Predonin is generally administrated for leucamia or other hematopoetic diseases as to inhibit the proliferation of pathologic marrow cells.

In case 2, anabolic steroid hormons were givsen for about 7 months. The authors did not find any further pathological appearance in roentgenograms of the skeleton which might be the effect of the hormon therapy. Also, case 1 and 3, Predonin and anabolic hormons were given respectively for 3.4 to 3.6 months and 3.0 to 3.4 months. These drugs were considered effective for the release of pain and general fatigue at least when

the disease was not so progressive.

SUMMARY

Recently numerous cases of multiple myeloma have been reported by the improvement of diagnostic procedures.

Here the authors are reporting three interesting cases of multiple myeloma.

Case 1. was given the exact diagonsis of multiple myeloma from the very rare happened pathologic fracture of the right radius. In this case, the extramedullary involvments of the heart, the hilar lymph nodes, the right lung, the intercostal muscles, the costal cartilage, and the diaphragm were revealed by the autopsy.

Case 2. was a diffuse type of myeloma which roentgenogram revealed slight osteoporosis in the spine but not typical punched-out radiolucencies in the skull or long bones. This case could be diagnosed by the bone marrow smear and the other laboratory data.

Case 3. was the rare instance in Japan which had been alive for three years since exactly diagnosed multiple myeloma.

Predonin and anabolic steroid hormons with or without chemotherapy were employed to these 3 cases, which effects would be assured at least in the improvement of the subjective symptoms.

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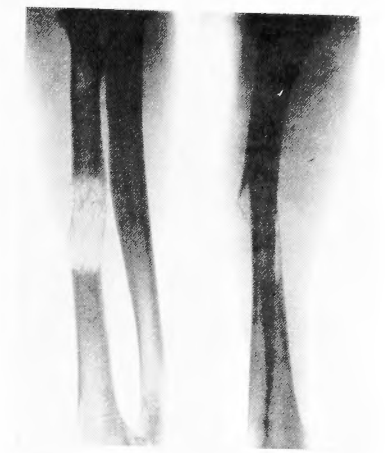
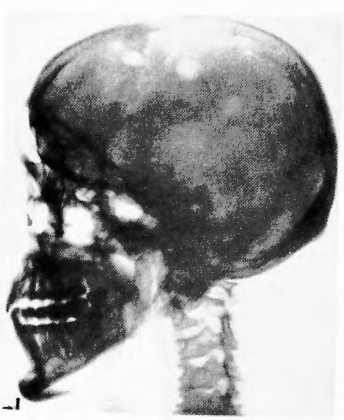
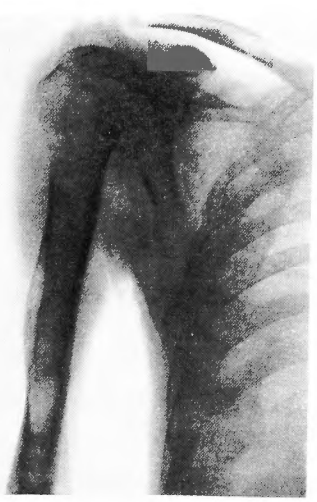


Fig, 1



Fig, 2



Fig, 3

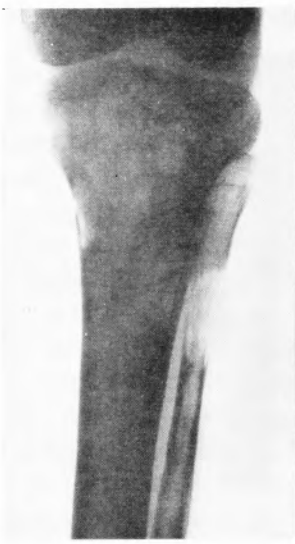
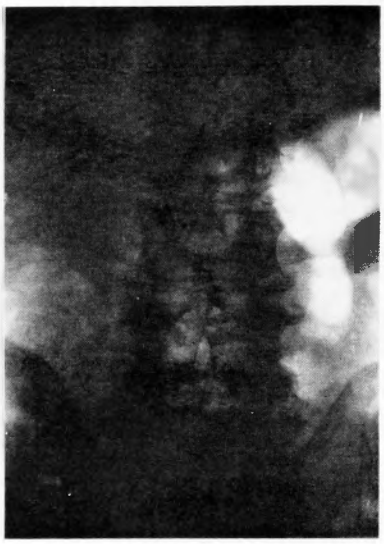
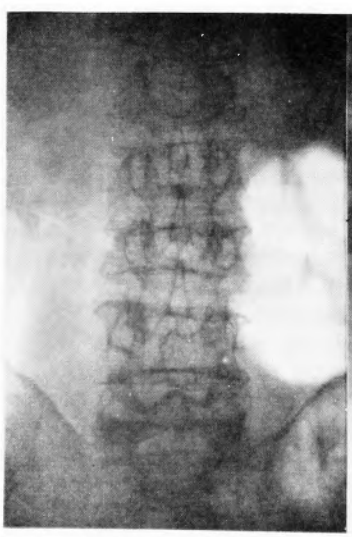


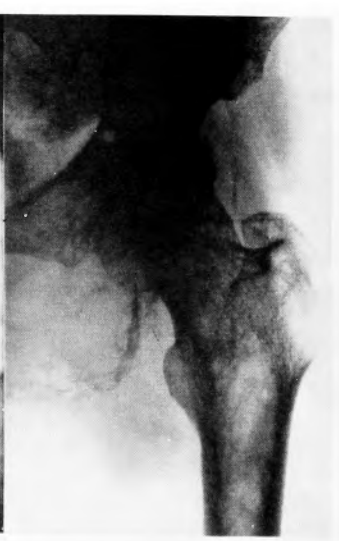
Fig. 4



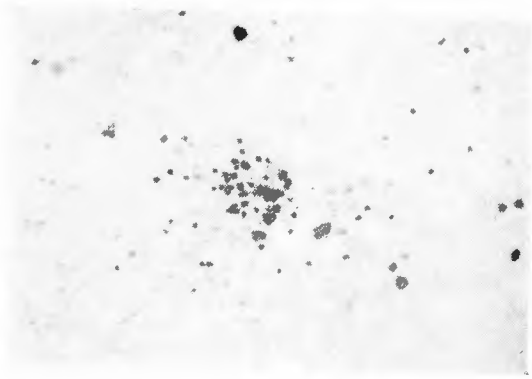
Fig, 5



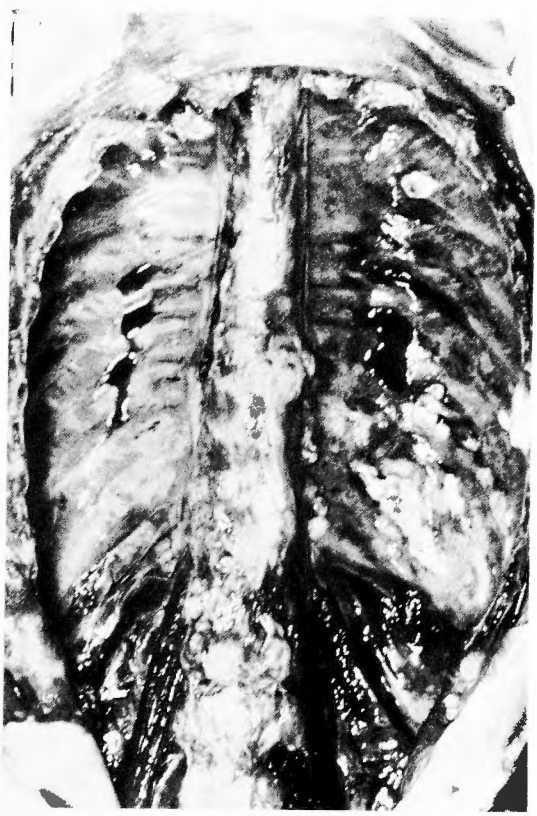
Fig, 6



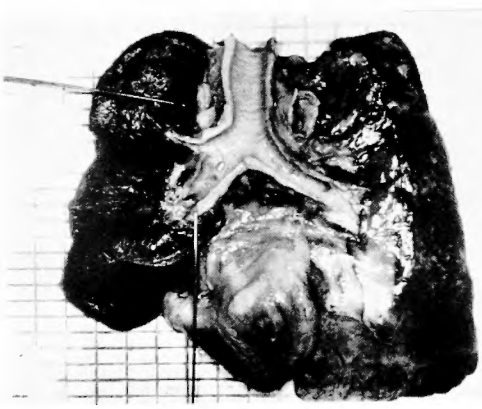
Fig, 7



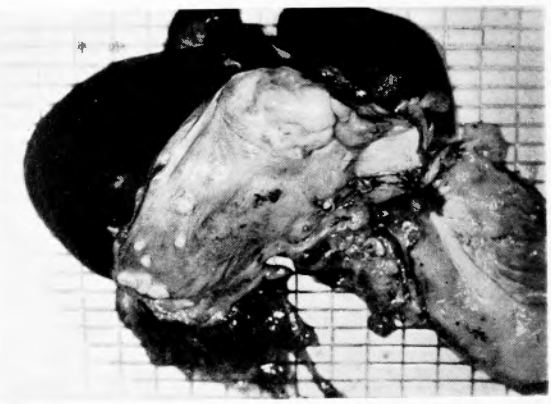
Fig, 8 Case 1 : Bone morrow smear



Fig, 9 Plasma cell infiltrations in the spine, the intercostal muscles and ribs



Fig, 10 Collaps of the right lung and hilar lymph node swelling



Fig, 11 Extraskeletal myelomatous infiltrations on the diaphragm

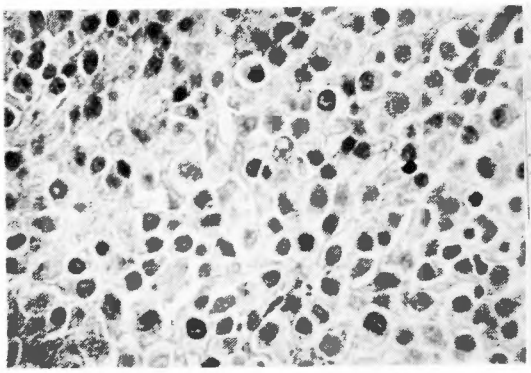
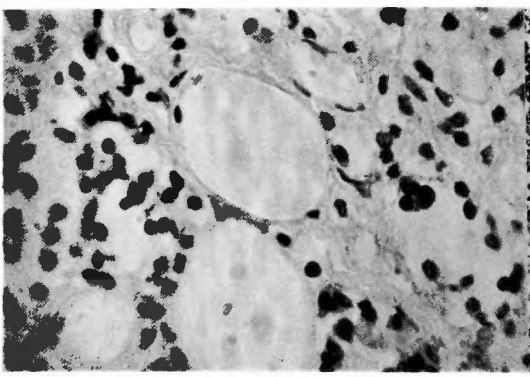
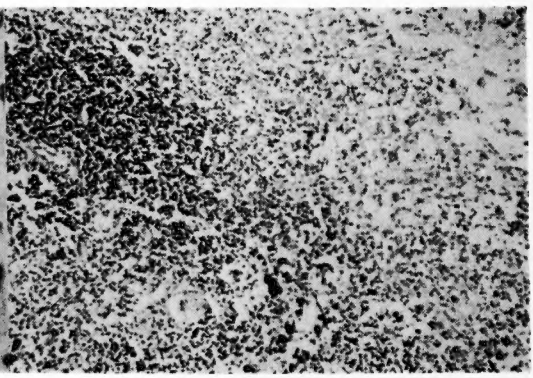


Fig. 12 Biopsy specimen

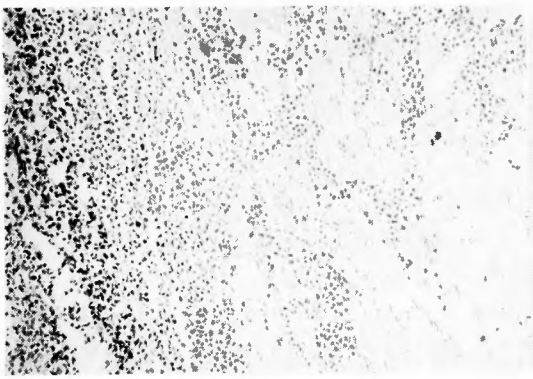
Fig, 13 Left lung



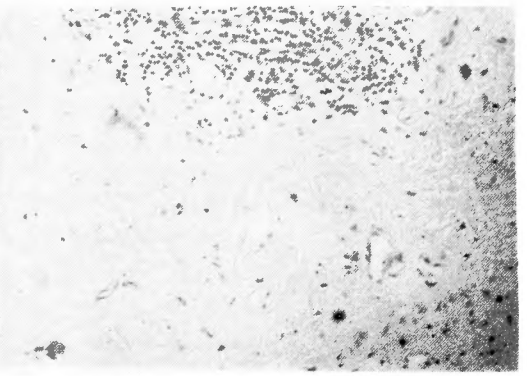
Fig, 14 Right lung



Fig, 15 Hilar lymph node



Fig, 16 Left ventricle



Fig, 17 Diaphragm

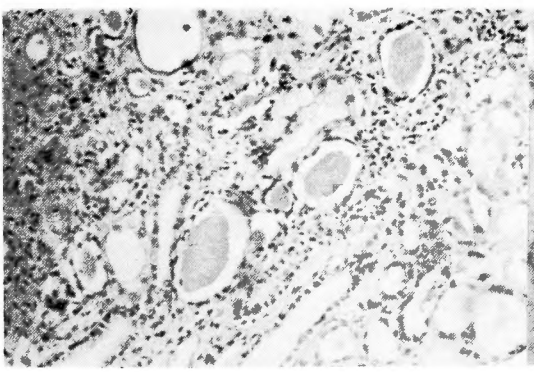
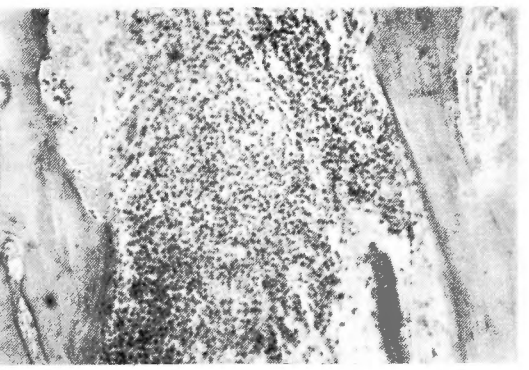
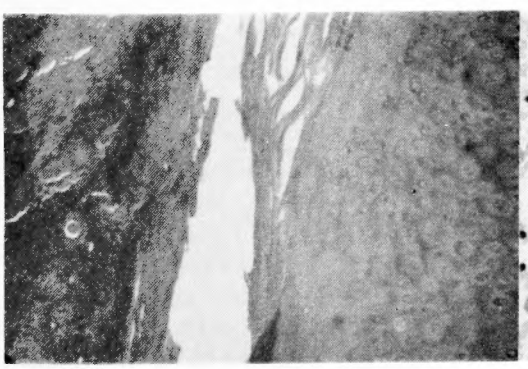


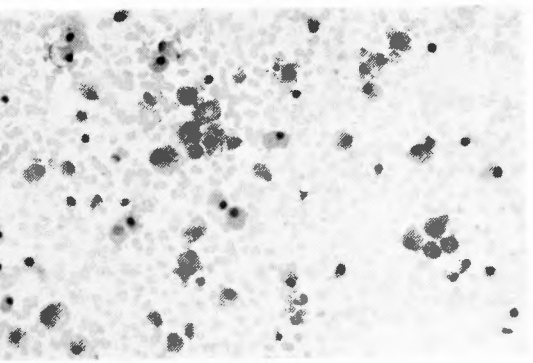
Fig. 18 Kidney



Fig, 19 Bone (Fibula)



Fig, 20 Intercostal cartilage



Fig, 21 Case 2: Bone marrow smear

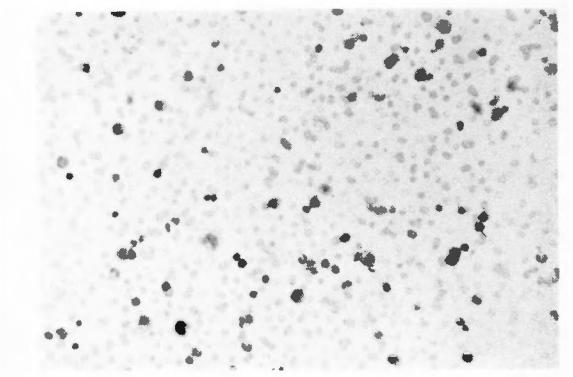


Fig. 22 Case 3: Bone marrow smear

和文抄録

興味ある多発性骨髄腫の症例

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多発性骨髄腫の報告は診断学の進歩と共に近年増加しつつある．われわれは本症の興味ある3例を経験したのでここに追加報告する．

われわれの症例は，今村らの分類に従えば，症例1および3が multiple myeloma，症例2が diffuse myeloma である．

症例1は右橈骨の病的骨折を契機として見出されたものである．本症の病的骨折は癌転移の場合の2倍の頻度を有するとされるが，長管骨ことに橈骨の病的骨折を初発症状とするものは本邦に於て極めて珍しい．また本症例では剖検によつて，心，肺門リンパ腺，右肺，肋間筋，肋軟骨，横隔膜などに多数の髄外侵潤を見出した．Extramedullary plasmacytoma と異なるこの髄外侵潤に関する記載は内外の文献とも乏しく，興味ある所見と考える．

症例2はレ線上脊椎に軽い骨粗鬆症を見出すのみで典型的な抜き打ち像がなく，骨髄穿刺その他の検査所見から診断されたもので，本症診察上かかる症例は注意する必要がある．

症例3は診断確定後3年間生存した症例であつて，文献上，とくにわが国に於いては2年以上生存する場合が少ないといわれる点からここに報告した．

これらの症例に対してわれわれは制癌剤の外に Durabolin, Orgabolin, Anadrol などの蛋白同化ホルモンと Predonin を投与した．若松らは本症患者に estrogen を投与して組織学的に治療傾向を認めており，われわれの症例2に於いてもその経過中レ線像の増悪は見られなかつた．これらの薬剤は少なくともその病勢が進行しない初期から末期以前に於いて，全身状態や疼痛に対して良影響を与えるものと考える．