Acta Medica Okayama

Volume 33, *Issue* 5 1979 *Article* 3

OCTOBER 1979

The tumor-forming type of multiple myeloma. I. Biological behavior.

Toshio Tanaka[*] Tatsuo Sezaki[†] Mineji Hujita[‡]

Akira Oka[**] Tsukasa Okamoto[††] Jishu Ito[‡‡]

[*]Okayama University,
[†]National Okayama Hospital,
[‡]Chugoku Central Hospital,
[**]Okayama University,
[††]National Fukuyama Hospital,
[‡‡]Kawasaki Hospital,

The tumor-forming type of multiple myeloma. I. Biological behavior.*

Toshio Tanaka, Tatsuo Sezaki, Mineji Hujita, Akira Oka, Tsukasa Okamoto, and Jishu Ito

Abstract

A total of 45 cases of multiple myeloma has been followed up clinically during the period from 7 to 80 months. Out of these, six patients (13.3%) were diagnosed to be the tumor-forming type; they developed discrete tumor formation at the disease onset or during clinical observation. Biological behavior of these cases is briefly outlined. Histologically, five cases presented with well or moderately well differentiated plasma cells according to the grading made by Pasmantier and Azar. The remaining one case was poorly differentiated in cell maturity, and with electron and immunofluorescence microscopies, proved to be of plasmacytic nature.

KEYWORDS: tomor-forming tupe, multiple myeloma

---

*PMID: 160183 [PubMed - indexed for MEDLINE]

Acta Med. Okayama **33**, (5), 359—370 (1979)

THE TUMOR-FORMING TYPE OF MULTIPLE MYELOMA
I. BIOLOGICAL BEHAVIOR

Toshio TANAKA, Tatsuo SEZAKI*, Mineji HUJITA**, Akira OKA***, Tsukasa OKAMOTO****, and Jishu ITO*****

*Pathology Section, Central Laboratories, Okayama University Medical School, Okayama 700; *Department of Medicine, National Okayama Hospital, Okayama 700; **Department of Medicine, Chugoku Central Hospital, Fukuyama 720; ***Department of Medicine (2nd Clinic), Okayama University Hospital, Okayama 700; ****Department of Pathology, National Fukuyama Hospital, Fukuyama 720; and *****Department of Pathology, Kawasaki Hospital Division, Kawasaki Medical School, Okayama 700, Japan*

Received March 23, 1979

Abstract. A total of 45 cases of multiple myeloma has been followed up clinically during the period from 7 to 80 months. Out of these, six patients (13.3%) were diagnosed to be the tumor-forming type; they developed discrete tumor formation at the disease onset or during clinical observation. Biological behavior of these cases is briefly outlined. Histologically, five cases presented with well or moderately well differentiated plasma cells according to the grading made by Pasmantier and Azar. The remaining one case was poorly differentiated in cell maturity, and with electron and immunofluorescence microscopies, proved to be of plasmacytic nature.

Key words: tumor-forming type, multiple myeloma

The mode of growth of multiple myeloma (MM) varies considerably as seen in leukemia, in which treatment schedules and optional drugs are precisely laid out accoreing to clinical as well as cytologic differences, *e.g.*, acute or chronic, and lymphocytic or granulocytic. In MM, the medullary and extramedullary are discerned from the localisation of lesions. In the former, according to the mode and distribution of tumor growth, one may categorize: 1) discrete nodular growth with solitary or multiple foci, 2) diffuse proliferation, 3) diffuse proliferation with multiple nodular growth, and 4) plasma cell leukemia. These distinctions are, however, arbitrary with considerable overlapping between discrete and diffuse tumor growth. We present here six cases of discrete nodular growth with solitary or multiple foci, *i.e.*, tumor-forming type.

CASE PRESENTATION

A total of 45 cases of MM patients is dealt with in the present work. Sixteen patients are still alive and have been followed up clinically during the period from 18 to 80 months, whereas 29 died at the 7th month in the shortest and 80th month in the longest. The patients with shorter clinical course than that period from the apparent onset of the disease were omitted from this survey. Out of these 45, six patients (13.3%) were diagnosed to belong to tumor-forming type; they developed discrete tumor formation at the disease onset or during clinical observation, and proved to have plasmacytoma histologically. These cases will be briefly described (Table 1).

Case 1. Ch. N. Female, born in December 1910, IgG (lambda). In the Spring of 1971, she noticed a thumb-tip-sized, subcutaneous nodule on the right forehead, followed by nasal congestion and gingival hemorrhage. On the admission to the Second Clinic of Medical Department, Okayama University Hospital (OUH) in January 1973, the forehead tumor measuring 5.5×7.5 cm, and a tumor protruding from the soft palate and extending to both cheeks were found. Under large, intermittent dose of melphalan, these tumors quickly decreased in size with disappearance of monoclonal immunoglobulin (M-protein). Towards the end of 1975, however, she was admitted to the Medical Department, National Okayama Hospital (NOH) because of the right facial paralysis and a walnut-sized tumor at the left nose with increasing M-protein. Chest x-rays revealed a rib-originated tumor measuring 6.5×5.5 cm in the right lower field. These tumors responded to ifosfamide (a derivative of cyclophosphamide) and later to melphalan followed by cyclophosphamide. In June 1978, an index finger-tip sized tumor appeared again on the left cheek and continued to enlarge; she has been followed up in outpatient clinic using cyclophosphamide.

Case 2. T. O. Male, born in July 1913, IgG (kappa). For about three years till 1973, he had had intra-articular aspiration and injection for the left gonalgia but without much effect. In November 1973, he was referred to the Orthopedic Department, OUH; from the suprapatellar through lateral aspect of the left thigh, there was a palm-sized, hard, tender tumor which appeared to adhere to the femur. X-rays revealed a periosteal reaction with spotted, atrophic radiolucency in the femur (Fig. 1). At the end of 1973, left hip disarticulation was done; histologically, reticulum cell sarcoma of the bone in a broad sense was diagnosed (Fig. 2). Later, as described below in detail, electron microscopic and immunofluorescence microscopic investigations confirmed a diagnosis of plasmacytoma (Figs. 3 & 4). In October 1975, at the second admission to the Medical Department, NOH, tumors measuring 6×7 cm each were noticed on the right anterior and left posterior sides of the thorax. Biopsy confirmed the

Table 1. Summary of six cases with tumor-forming type of MM

	Patients					
	Ch. N.	T. O.	H. K.	M. K.	M. S.	M. T.
Disease onset (Age)	61	60	55	82	68	69
Sex	F	M	M	M	M	M
Immunoglobulin	IgG, lambda	IgG, kappa	IgG, lamda	IgG, lambda	IgG, lambda	IgG, kappa
Punched-out lesions by X-rays[a]	Skull	L. femur	Pelvis	None	Skull	Skull
Tumor-forming sites	Head, Soft palate	Both chest wall	R. gluteal, R. inguinal	R. chest wall	Head, Larynx	Head, Breast, R. chest wall, etc.
Plasma Cells in						
Bone marrow (%)	2.4	2.0	16.8	2.0	0.4	11.2
Histologic grading	B	C	A	B	A	A
Drugs used[b]	1. Mel 2. Ex	1. Mel+SH 2. VCR+SH+Ex	1. Mcl 2. If or Ex	1. Mel 2. If 3. SH	1. Mel+SH+If	1. Mel+SH+ff 2. Radiation 3. Others
Therapeutic effect						
M-protein	1. 100		1. 53	1. 71	1. 100	1. 79
Reducing rate[c] (%)	2. 100	2. 70	2. 75			
Bone X-rays	Calcified	—	Calcified	—	Calcified	Calcified
Tumor[c]	1. Disapprd[d].	2. Disapprd.	1. Disapprd.	1. Disapprd. 2. Disapprd.	1. Disapprd.	1. Disapprd. or Reduced to less than 50%
Surviving time[e] (months)	More than 72 (Alive)	53 (Dead)	26 (Dead)	11 (Dead)	More than 25 (Alive)	20 (Dead)

a Usually, larger punched-out lesions were surrounded by smaller punched-out lesions.
b Numerals, 1, 2 and 3, indicate major therapeutic trials. Drugs underlined were effective on the patients. Mel: Melphalan, Ex: Cyclophosphamide, SH: Steroid hormone, VCR: Vincristine, If: Ifosfamide.
c Numerals, 1 and 2, indicate the effect of major therapeutic trials.
d Disapprd; disappeared.
e Period from the time for initiating chemotherapy to December 1978.

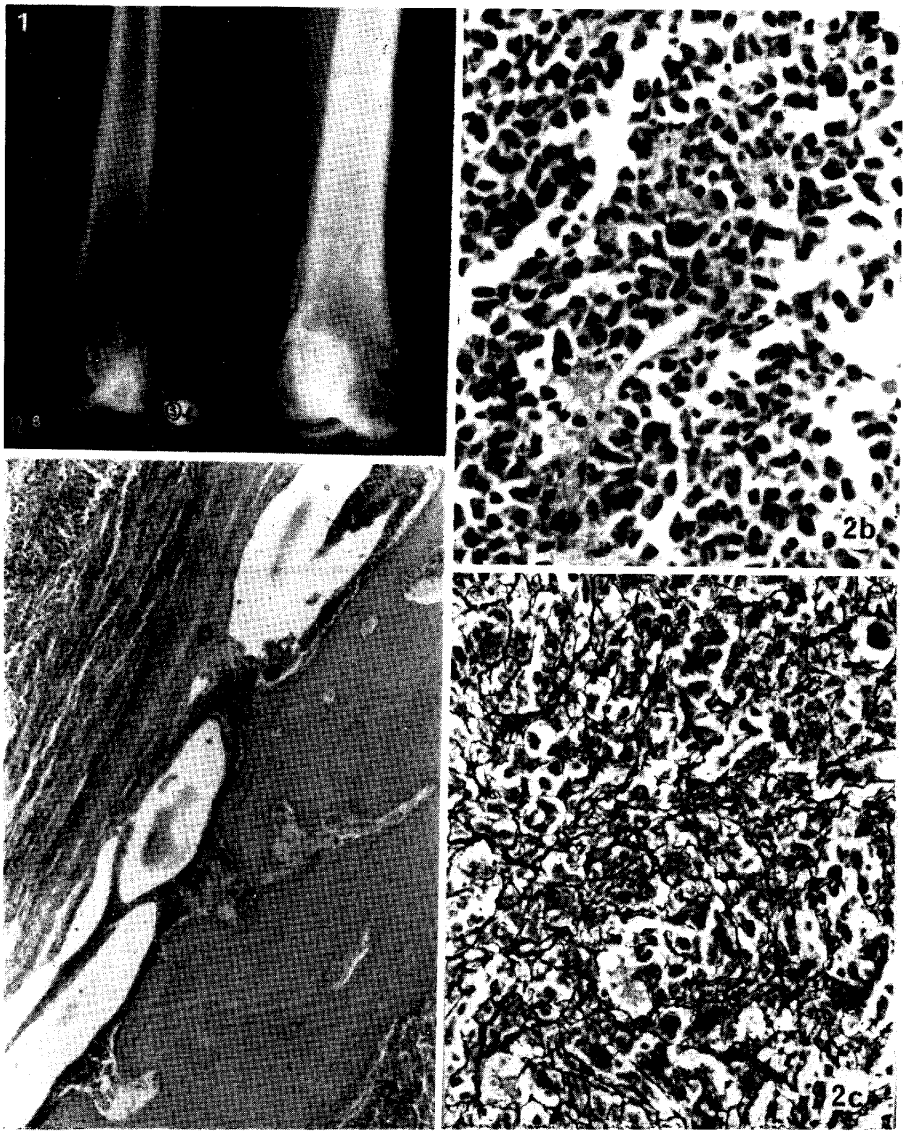
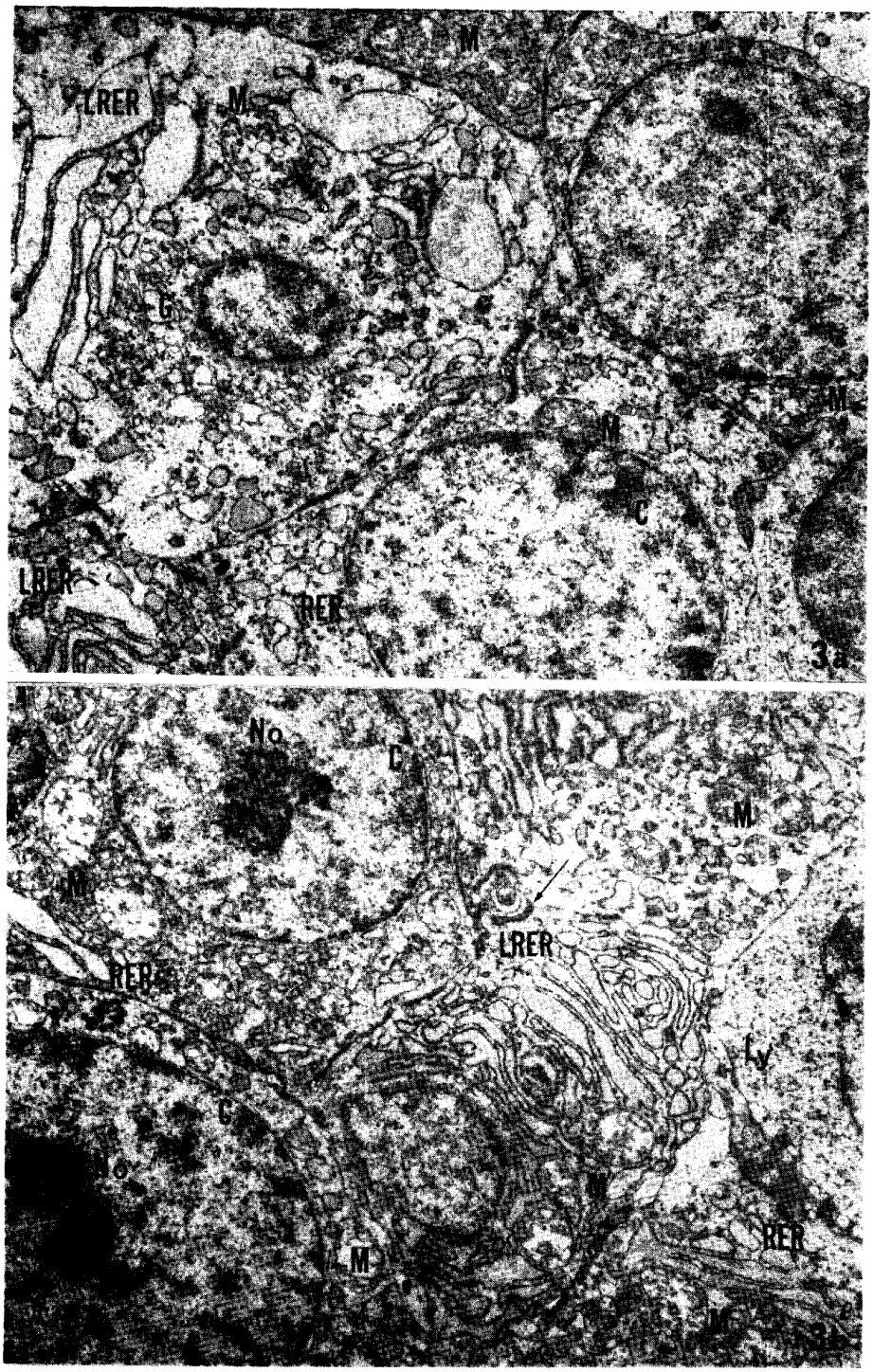
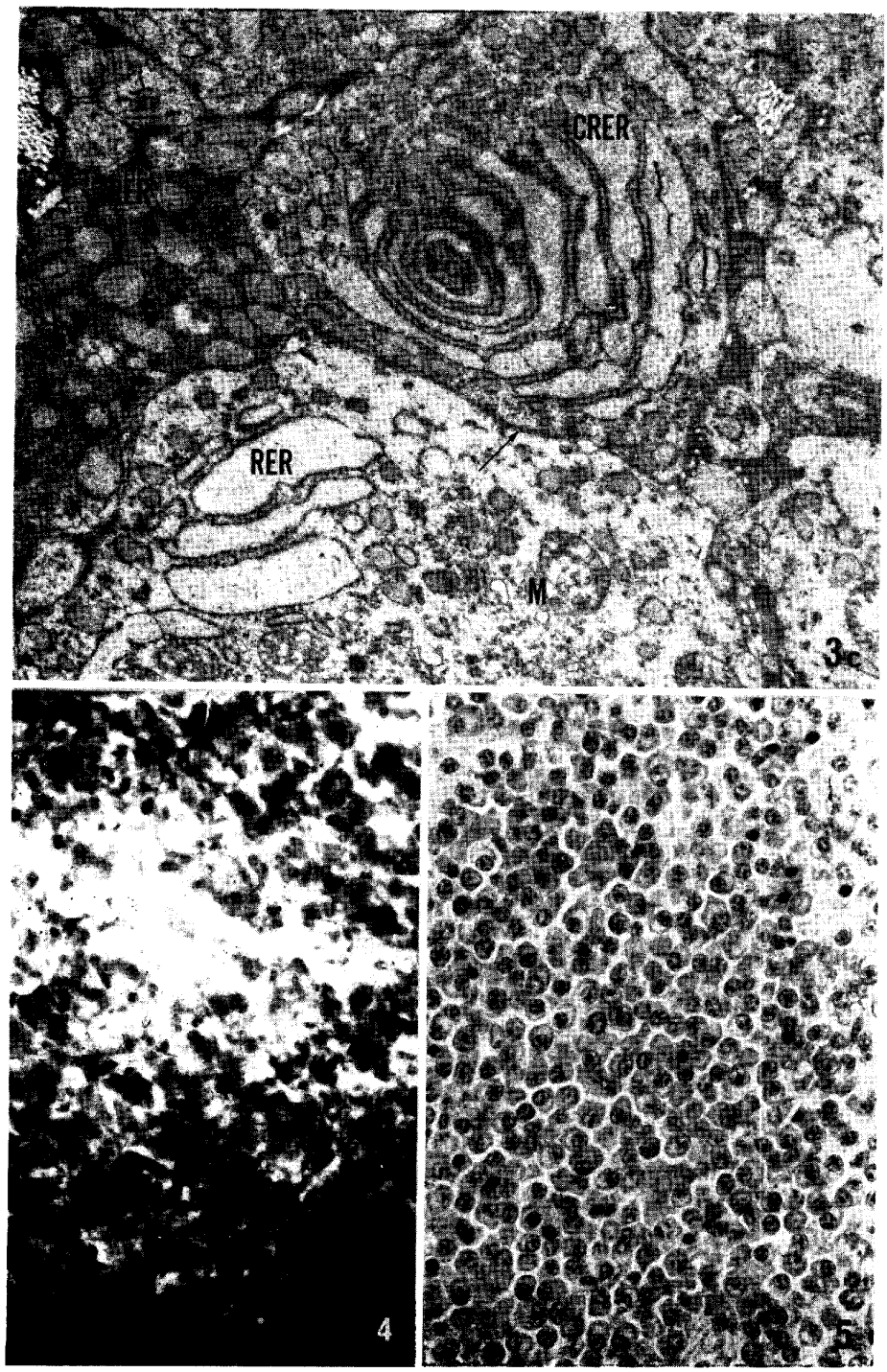


Fig. 1. X-ray finding of the left femur (case 2) showing a periosteal reaction with spotted atrophic radiolucency.

Fig. 2. Histology (case 2) showing poorly differentiated cells resembling reticulum cell sarcoma. 2a: Tumor growing outside the periosteum (P). HE, ×40. 2b: Variegated morphology of tumor cells with a few giant cells. HE, ×400. 2c: Well-developed reticulin fibers surrounding a single or a few tumor cells. Silver, ×400.

Fig. 3. Electron micrographs (case 2). 3a: Two immature cells in the right upper and lower, and one intermediate cell in the left upper field. ×9,200. 3b: Two immature cells in the left upper and lower, and one mature cell in the center, ×9,200. 3c: One each of intermediate and mature cells in the middle lower and upper fields, respectively. ×13,800. No: Nucleolus, C: Chromatin, RER: Rough-surfaced endoplasmic reticulum, M: Mitochondrion, G: Golgi's apparatus, Ly: Lymphocyte, and an arrow indicating electron-dense, amorphous material in the intercellular space.


M
LRER
M
G
M
M
C
LRER
RER
3a
No
C
M
M
LRER
RER
Ly
C
Ly
M
RER
M
M
3a


CRER
RER
M
3
4
5

diagnosis of plasmacytoma, which responded to an intermittent administration of cyclophosphamide. Around September 1977, at the fourth admission, chest x-rays revealed multiple tumor shadows corresponding to the bilateral 7th to 8th ribs; these responded quickly to cyclophosphamide and combined procarbazine, vincristine and prednisone, followed by melphalan. With gradual increase of M-protein and nodule formation on the dorsum, in October 1978 the patients died. Autopsy was not performed.

Case 3. H. K. Male, born in July 1919, IgG (kappa), BJ (kappa). Around 1971 he developed lumbago, and in September 1975 gait disturbance due to pain in the right gluteal region. In August 1974 when admitted to a local hospital, there was a child's head-sized tumor on the left gluteal region, of which biopsy confirmed plasmacytoma (Fig. 5). The tumor responded markedly to combined melphalan and prednisone together with decrease of M-protein. Later in October 1975, the tumor became larger than before treatment, and was treated with combined melphalan, ifosfamide and prednisolone with good response. In October 1976, he was transferred to NOH. Roentgenologically, the 11th thoracic and 5th lumbar vertebrae were destroyed and compressed apparently due to tumor infiltration, and also almost entire left pelvic bone was lysed leaving only a marginal area. The latter x-ray finding was consistent with a continuous growth of the left gluteal tumor into the pelvic cavity by breaking through the pelvic bone. Soon after the admission, the patient died; autopsy was not performed.

Case 4. M. K. Male, born in July 1891, IgG (lambda), BJ (lambda). Soon after admission to the Second Medical Department, OUH, in August 1973, the patient rapidly developed paralysis of both lower extremities with ascending sensory disturbance. Through administering large, intermittent doses of melphalan, M-protein decreased and the sensory disturbance descended. In January 1974, a tumor appeared on the right chest wall; this was proved to be plasmacytoma histologically and had enlarged up to fist size, once again with ascending sensory disorder and increasing M-protein, all of which responded to four courses of ifosfamide. Around June 1974, the above neurologic symptoms worsened and M-protein increased, and in August of the same year, the patient died. Post-mortem examination revealed metastasis in the vertebrae, right ribs, right thoracic wall, both adrenal glands and tracheo-bronchial lymph nodes.

Case 5. M. S. Male, born in September 1908, IgG (lambda). In November 1976, the patient was admitted to the Medical Service, NOH, due to a

Fig. 4. Immunofluorescent micrograph (case 2) showing anti-human IgG-labeled fluorescence in tumor cells. ×200.

Fig. 5. Specimen (case 3) biopsied from the left gluteal region showing well-differentiated plasma cells. HE, ×400.

fist-sized, subcutaneous tumor on the left temporal area, and a tumor of 3.5 cm in diameter on the right vocal cord which had caused hoarseness and dyspnea. Before the admission, these tumors had already been biopsied, and the patient was unable either to speak or swallow because of tracheostomy. In December of the same year, alternative chemotherapy consisting of melphalan, ifosfamide and prednisolone was initiated. Two weeks later these tumors disappeared, and after 4–5 weeks he regained the speech and swallowing with disappearance of M-protein and calcification and size reduction of the radiolucency corresponding to the cranial tumor. A year later, in December 1977, however, he developed a tumor in the right hilus. This has been controlled with Lineac x-ray irradiation, and the patient is alive and well at present.

Case 6. M. T. Male, born in November 1906, IgG (kappa). In November 1975, when the patient was admitted to the Medical Department, NOH, there were three prominent tumors; a walnut-sized nodule on the right frontal area which infiltrated into the right orbit with subsequent protrusion and downward displacement of the right eyeball and visual disturbance (Fig. 6), another tumor of 5×4 cm on the left forechest corresponding to the 3rd to 4th ribs, and the third, a man's fist-sized tumor which protruded into the left upper part of the lung field by x-rays (Fig. 7). Biopsy of the right frontal tumor showed a plasmacytoma. Two weeks after commencing a combined therapy of melpha-

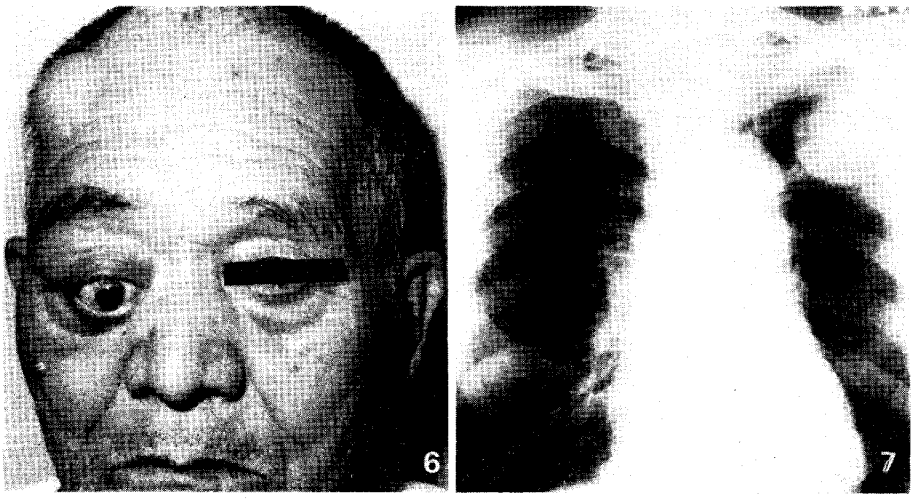


Fig. 6. Patient's outlook (case 6) showing a tumor on the right frontal area which infiltrated into the right orbit with subsequent protrusion and downward displacement of the eyeball.

Fig. 7. Roentgenogram (case 6) showing a tumor protruding into the upper left of the lung field.

lan, ifosfamide and prednisolone, M-protein decreased, visual disturbance and eyeball protrusion improved, and the left forechest tumor disappeared. By six weeks later, the right frontal and the left intrathoracic tumors had decreased in size, and eight weeks later skull x-rays showed a reduced radiolucency with focal calcification (Fig. 8). In December 1976, due to multiple nodules involving both breasts and subcutis of the forechest and abdomen (Fig. 9), various combination therapies, including carmustine, vincristine, prednisolone, procarbazine,

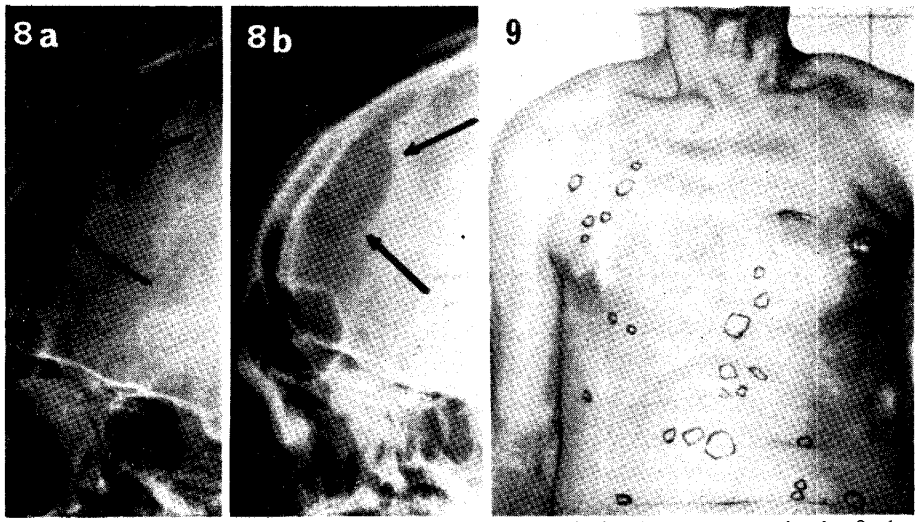


Fig. 8. Skull x-rays (case 6) indicating a punched-out lesion (arrows) seen in the 8a before treatment, and the same lesion in the 8b with reduced radiolucency with focal calcification after the treatment.

Fig. 9. Multiple subcutaneous nodules indicated by circles (case 6) involving the forechest, abdomen and left breast; the right breast had been amputated previously because of tumor infiltration.

neocarzinostatin and cytosine arabinoside, were attempted, but without much effect. These tumors then disseminated all over the skin with rapidly increased M-protein, and the patient died in June 1977. Necropsy disclosed extensive nodular metastasis to mediastinal, mesenteric and retroperitoneal lymph nodes, both adrenal glands, pancreas, atrial septum, left lower lobe of lung, left kidney, thyroid and bone marrow; the adrenals and pancreas were almost entirely replaced by the tumor.

ELECTRON AND IMMUNOFLUORESCENT MICROSCOPIC FINDINGS

The specimen was obtained from the amputated left femur of the case 2 (T. O.).

Electron microscopic observation. According to cell maturity, we were able to classify tumor cells into three major types. 1) Immature cells (Fig. 3, a & b): These were somewhat larger than mature lymphocytes infiltrating in the tumor, and had a large nucleo-cytoplasmic ratio. The nucleus was not eccentrically located, was round or oval in shape, and was smooth in contour with condensed chromatin along nuclear membrane and often prominent nucleoli. Cytoplasm was often polygonal in shape, rich in large mitochondria and vesicular rough-surfaced endoplasmic reticula (RER), and poor in free ribosomes. The RER were only slightly elongated though not lamellated, and contained a low electron-dense, fluid substance. This type of cell hardly possessed a plasmacytic feature. 2) Intermediate cells (Fig. 3, a & c): These showed remarkably enlarged cytoplasm with a subsequently decreased nucleo-cytoplasmic ratio. RER developed considerably well often with cystic dilatation or elongation and focal lamellar arrangement. The Golgi complex was also well developed. This type of cell somewhat resembled plasma cells. 3) Mature cells (Fig. 3, b & c): The nucleus was in general located eccentrically, although nuclear chromatin did not show a clear-cut wheel-spoke pattern. Cytoplasm was filled with well-developed RER which were irregularly or circularly lamellated. The plasmacytic nature was almost evident in this type of cell. In the intercellular space, electron-dense, amorphous material often appeared to coat the cytoplasmic membrane. Neither Russell's bodies nor other inclusion bodies were identified in cytoplasm or nuclei. Apart from these three types of cells, there were also various maturing stages of cells which could be traced one another with ease.

Immunofluorescent microscopic observation (direct method). Anti-human IgG-labeled fluorescence was identified in almost all the tumor cells, especially in cytoplasm although some in nucleus (Fig. 4). The intracytoplasmic fluorescence appeared diffuse or granular in its distribution, whereas intranuclear fluorescence was dotted or slightly diffuse. Its intensity varied in degree depending on each tumor cell, and was more prominent in rather matured plasmacytic cells compared to less matured cells. Fluorescence was present also intravascularly in the interstitium of tumor tissue. The fluorescence was proved to be specific, because it markedly decreased in its intensity with the blocking test.

DISCUSSION

According to a survey in 1972 made by Imamura (1), the overall death rate from malignant tumors was 120.4 against one hundred thousand of Japanese population; this figure ranked the second after cerebrovascular accidents. Among these, cases died of malignant tumors originating from the hemopoietic organs amounted to 7,027; this included mostly various types of leukemia followed by malignant lymphomas. This figure occupied 5.5% of all malignant

tumors, and coorresponded to 6 6 against one hundred thousand of the population. Out of the above 7,027, 604 patients (8.6%) died of MM, *i.e.*, 0.57 against one hundred thousand. Briefly, 120.4, 6.6 *vs.* 0 57 per one hundred thousand of Japanese died of all malignant tumors, hemopoietic malignancies and MM, respectively. The overall death rate for MM has tended to be increased since around 1958, when its death rate indicated less than 3.5% among all hemopoietic malignancies; incidentally, about that time, electrophoretic techniques started to spread widely for clinical use.

According to our survey, the tumor-forming type of MM occupied approximately 10% of all types of MM. Therefore, this type of MM is indeed very rare as compared to overall incidence of hemopoietic malignant tumors. This type, however, certainly causes pain or motor distubance due to compression or destruction of the organs by tumors, as well as, depending on the originating sites, visual, respiratory or neurologic disturbance. Moreover, it forms extramedullary tumors in various vital organs. On the other hand, compared to other types, this type tends to manifest localized tumor proliferation, and to produce M-protein of IgG with predominant lambda type.

Concerning cell maturity, the tumor can be graded in three based on the dominant cells type, as proposed by Pasmantier and Azar (2). Grade A or differentiated myeloma resembles reactive plasma cells, grade C represents poorly differentiated myeloma cells, and grade B represents an intermediate form of the above two. Accordingly, we were able to grade our cases into three cases of A, two of B, and one of C. There was, however, no apparent relation between the histologic grading and clinical course, although admittedly the number of cases was too few to draw any conclusions, so far. As stated before, initially it was difficult to make a diagnosis on the patient, T. O. (case 2); we made an arbitrary diagnosis of reticulum cell sarcoma of the bone in a broad sense. Later, however, electron and immunofluorescence microscopies identified the tumor to be plasmacytic nature. In fact, cells in this tumor appeared so poorly differentiated light microscopically that we hardly escaped the conclusion of mere reticulum cell sarcoma. This case can be classified histologically as grade C, and can be categorized as a plasmacytic reticulum cell sarcoma by Okano, Azar and Osserman (3) or plasma cell reticulosarcoma by Holt and Robb-Smith (4). In addition, according to the hypothesis put forward by Salmon and Seligmann (5), the presence of a variant of this type in MM may support the view that the tumor is composed either of Bo stage of cells (or B stem cells) or of B2 cells (or immunoblasts).

Acknowledgment. The work was supported in part by a Grant-in-Aid for Cancer Research (Grant No. 51-4) from the Ministry of Health and Welfare of Japan.

REFERENCES

1. Imamura, Y.: Multiple myeloma—an epidemiologic study according to death statistics. *Igaku-no-Ayumi* **90**, 670-678, 1974 (in Japanese).
2. Pasmantier, M. W. and Azar, H. A.: Extraskeletal spread in multiple plasma cell myeloma. A review of 57 autopsied cases. *Cancer* **23**, 167-174, 1969.
3. Okano, H., Azar, H. A. and Osserman, E. F.: Plasmacytic reticulum cell sarcoma. Case report with electron microscopic studies. *Am. J. Clin. Pathol.* **46**, 546-555, 1966.
4. Holt, J. M. and Robb-Smith, A. H. T.: Multiple myeloma: Development of plasma cell sarcoma during apparently successful chemotherapy. *J. Clin. Pathol.* **26**, 649-659, 1973.
5. Salmon, S. E. and Seligmann, M.: B-cell neoplasia in man. *Lancet* **ii**, 1230-1233, 1974.