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Diffuse Infiltration of Bone Marrow by Tumor Cells*

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Bone marrow examination is a routine procedure in children with tumors because infiltration of the bone marrow,if present, is helpful in the differential diagnosis of malignant neoplasms. The most common solid tumors producing bone marrow metastases in children are neuroblastoma, retinoblastoma, and rhabdomyosarcoma.[2, 3, 8, 10] and the degree of involvement varies from a few sacttered clumps of tumor cells to complete replacement of the normal marrow element. Although one of the earliest report[6] of bone marrow infiltration proven by aspiration in Anglo-American literature was of a two and a half year-old boy with neuroblastoma in whom the infiltration was presented as complete replacement of marrow elements, this is presumably rare.

For this reason we wish to report nine cases of neuroblastoma and one of retinoblastoma in which bone marrow aspirations revealed complete replacement of normal marrow elements by tumor cells (Figure 1, 2, 3). As a matter of fact, because of the considerable increase in the number of immature cells, and/or blasts in the peripheral smear with marked thrombocytopenia and/or severe anemia, a diagnosis of leukemia was entertained at the outset in eight of the cases.

Materials and Methods

The patients were six males and four females ranging in age from three weeks to nine years. Their complaints, positive physical, roentgenographic, and pertienent laboratory findings are summarized in

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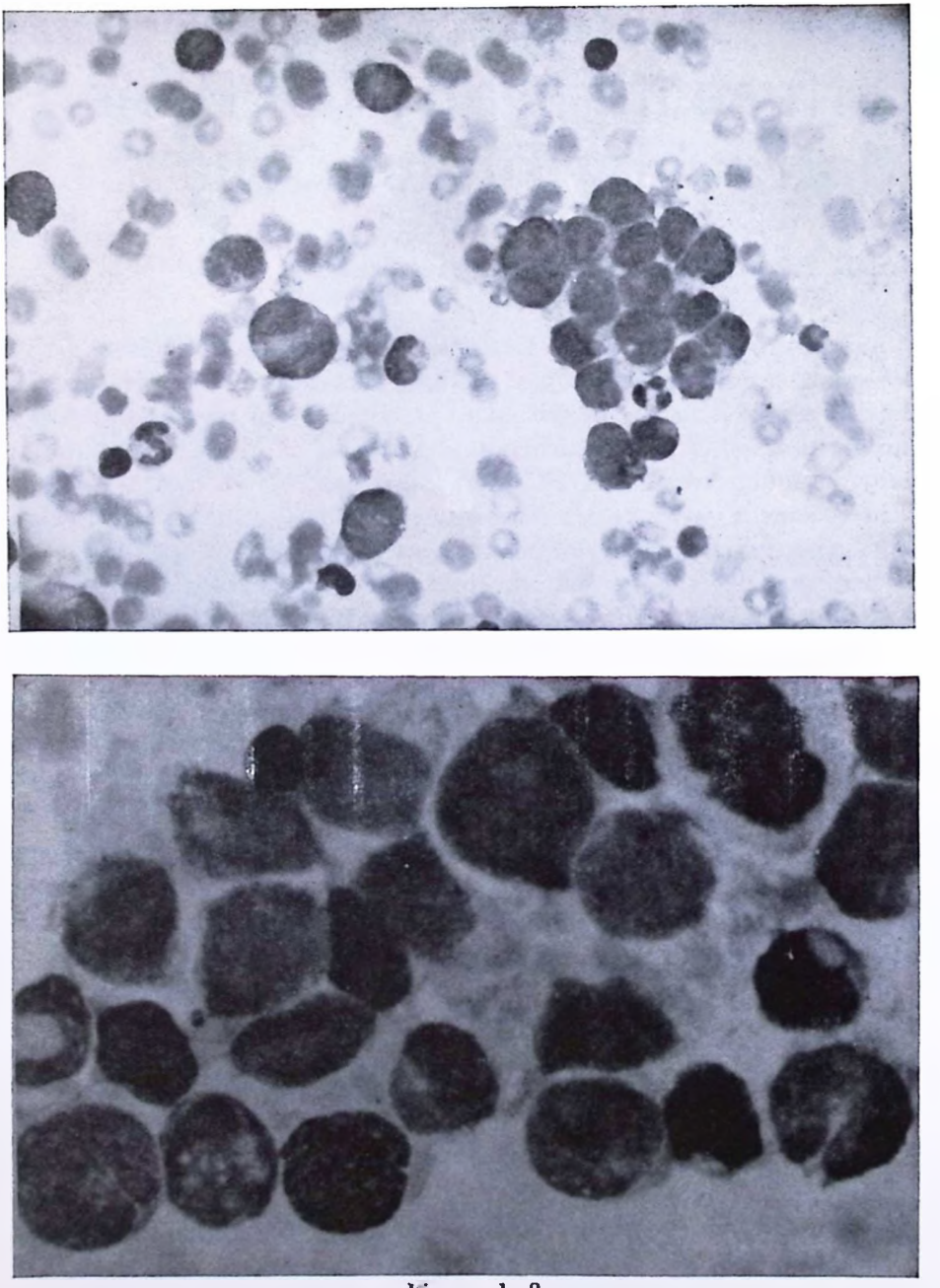

Figure 1 - 2

Rosette formation of neuroblastoma cells in bone marrow

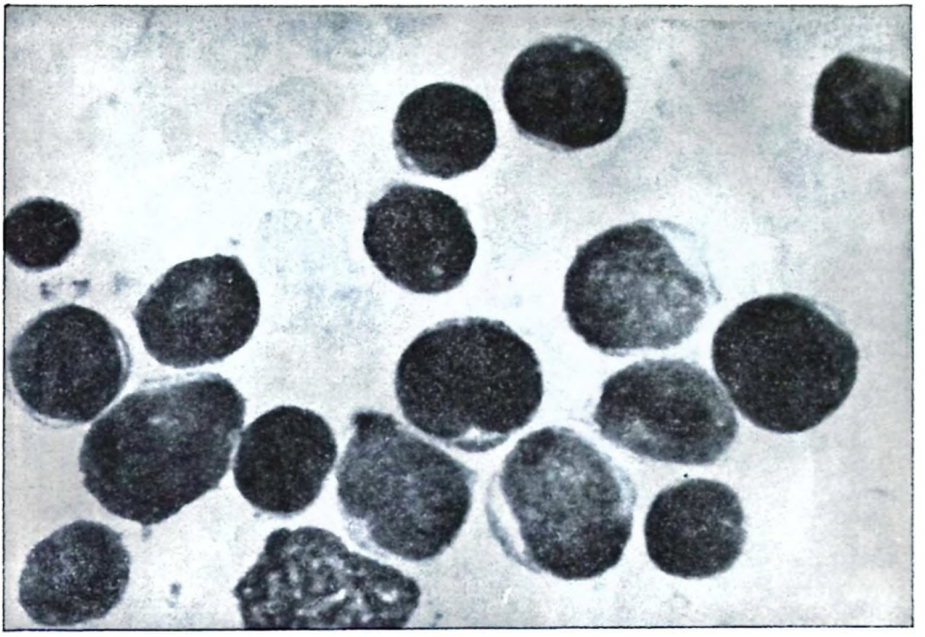

Figure 3

Bone marrow infiltration by neuroblastoma cells like leukemia

Table I, the hematologic data in Table II. For seven of the patients the diagnosis was confirmed by histologic examination. In the remaining three, the diagnosis was based on evaluation of vanillin mandelic acid (VMA) excretion (in two), IVP changes (in two), roentgenographic changes (in two), and clinical and bone marrow studies.

Bone marrow aspirates were obtained from the iliac crest (from the tibia of one 3 week-old child) using an 18 or 20 guage needle and slides were stained with Wright's stain. Hemograms were done following standard technique, hemoglobin concentrations were determined by the cyanmethemoglobin method, and VMA excretions were determined according to the method described by Gitlow et al.[5]

Discussion

Neuroblastoma, the most common of the childhood malignant tumors, is the one which most frequently metastasizes bone in marrow.[2, 3, 8, 10] The cell morphology and syncytial masses are generally accepted as characteristic of this tumor, but diffuse infiltration of bone marrow has also been reported.[2, 4, 6, 7] In seven of our patients, initial aspiration of the marrow on admission revealed diffuse infiltration by tumor cells.

TABLE I

PERTINENT CLINICAL, PHYSICAL FINDINGS AND LABORATORY DATA

No.	Age (years)	Sex	Presenting clinical Findings	Plalpable abdominal mass	Radiological Findings	Changes in I.V.P.	Histopathological Diagnosis	V.M.A γ/mgm creatin.
I	9	F	Fever, abdominal distension	Present	Metastasis in bone	+	Neuroblastoma (abdominal lymph node)	9.6
II	9	M	Weakness, pallor. pain in legs	Not present	Mestastasis in bone, calcification in abdomen	+	None	11.6
III	2.5	M	Abdominal distension and pain	Present	No abnormality	+	None	2.4
IV	3.5	M	Pallor, exophthalmos, ecchymosis on body, pain in legs, inability to walk	Not present	Metastasis in bone	None	None	8.6
V	4	M	Exophthalmos, pain in knees	Not present	Mass in anterior mediastinum	None	Neuroblastoma (cervical lymph node)	4.8
VI	6	M	Pallor, nose bleeding, exophthalmos	Not present	Metastasis in bone	None	Neuroblastoma (orbita)	–
VII	2	F	Exophthalmos	Not present	Metastasis in bone	None	Neuroblastoma (orbita)	–
VIII	3	F	Exophthalmos, abdominal distension	Not present	Metastasis in bone	None	Neuroblastoma (orbita)	–
IX	3 wks	M	Pallor, skin nodules, abdominal distension	Present	No abnormality	+	Neuroblastoma (skin nodules)	–
X	3	F	Exophthalmos	Not present	No abnormality	Not done	Retinoblastoma (palpebra)	–

TABLE II

HEMATOLOGICAL FINDINGS

No.	Hemoglobin (gm/100 ml)	WBC per cumm	Thrombocytes per cumm	Differential	Bone Marrow
I	6.5	15,400	abundant	60 Neut. 40 Lym.	Cellular
II	3.95	7,800	48,000	4 Neut. 82 Lym., 14 Bla.	Hypocellular
III	9.6	7,400	abundant	56 Neut. 42 Lym., 2 Eos.	Cellular
IV	6.25	5,500	80,000	60 Neut. 32 Lym., 8 Mye.	Cellular
V	12.5	9,000	few	50 Neut. 28 Lym. 4 Mye. 18 Bla.	Cellular
VI	3.14	24,000	44,000	47 Neut., 40 Lyo., 13 Nor.	Cullelar
VII	13.26	32,000	few	16 Neut., 50 Lym., 34 Bla.	Cellular
VIII	3.46	10,600	284,000	52 Neut., 46 Lym., 2 mye.	Cellular
IX	9.15	6,000	abundant	60 Neut., 26 Lym., 12 Nor., 2 Bla.	Cellular
X	10.16	15,600	few	32 Neut., 54 Lym., 6 Mye., 8 Bla.	Cellular

(Neut= Neutrophil; Lym= Lymphocyte; Mye= Myelocyte; Nor= Normoblast; Eos= Eosinophil; Bla= Blast like cells

In two (No: V and VII) infiltration was not discovered until 19 days and 5 months, respectively, after the diagnosis was established, when bone marrows were done because of immature cells and thrombocytopenia in peripheral smears (Figure 4, 5.)

Although it is generally accepted that blasts of solid tumors do not appear in peripheral circulation[4, 10] there are contradictory reports.[1, 6, 7] Three of our patients had 12-24 % and one 2% blast-like cells in the peripheral smear. Normoblasts and young myeloid elements were also present in the smears of five of the nine patients. Despite diffuse marrow infiltration, there were no bony changes in the X-rays of three of our nine patients. This finding agrees with previous reports that bone marrow infiltration by neuroblastoma may occur without X-ray changes of bones[2, 3, 9, 10]

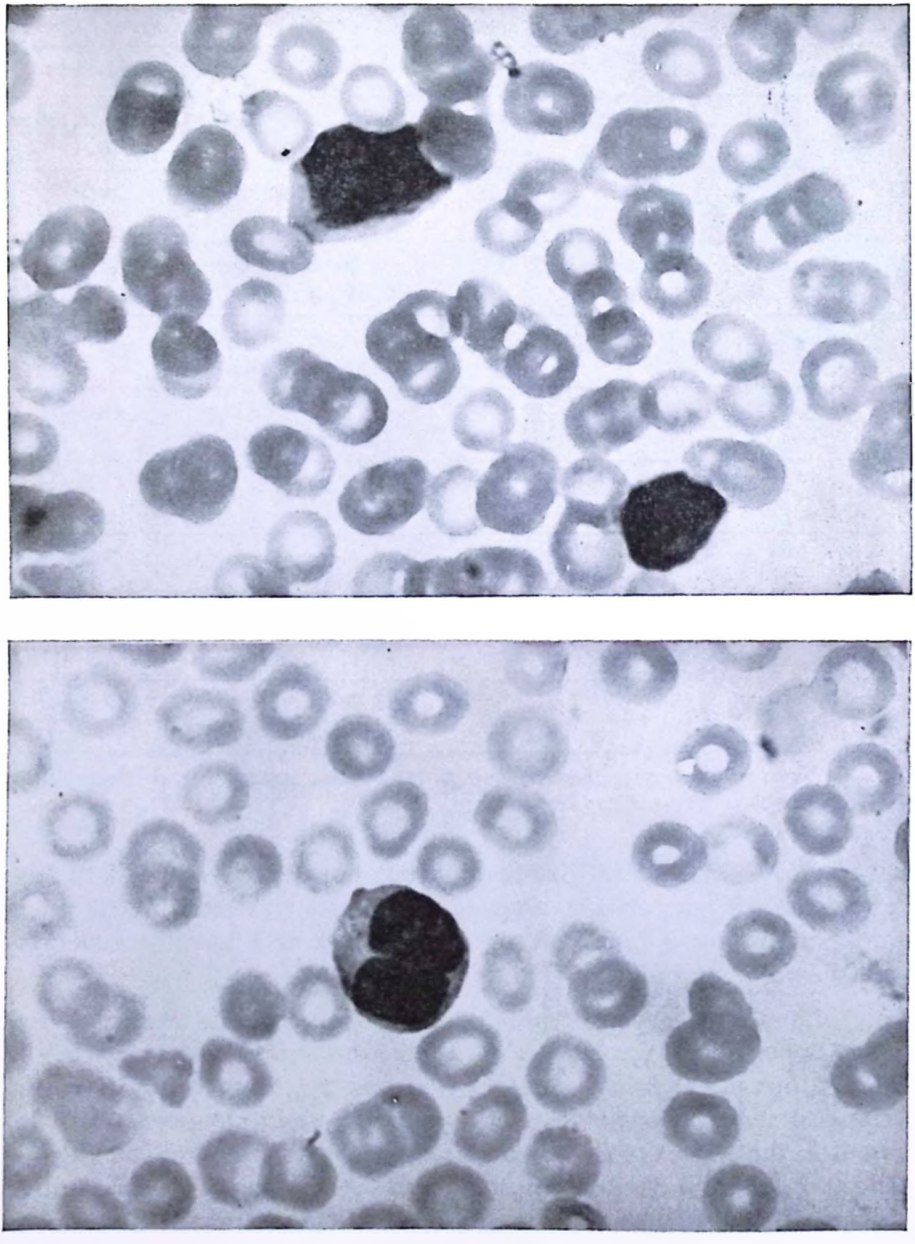

Figure 4-5

Peripheral smear: Shows blasts and no platelets seen

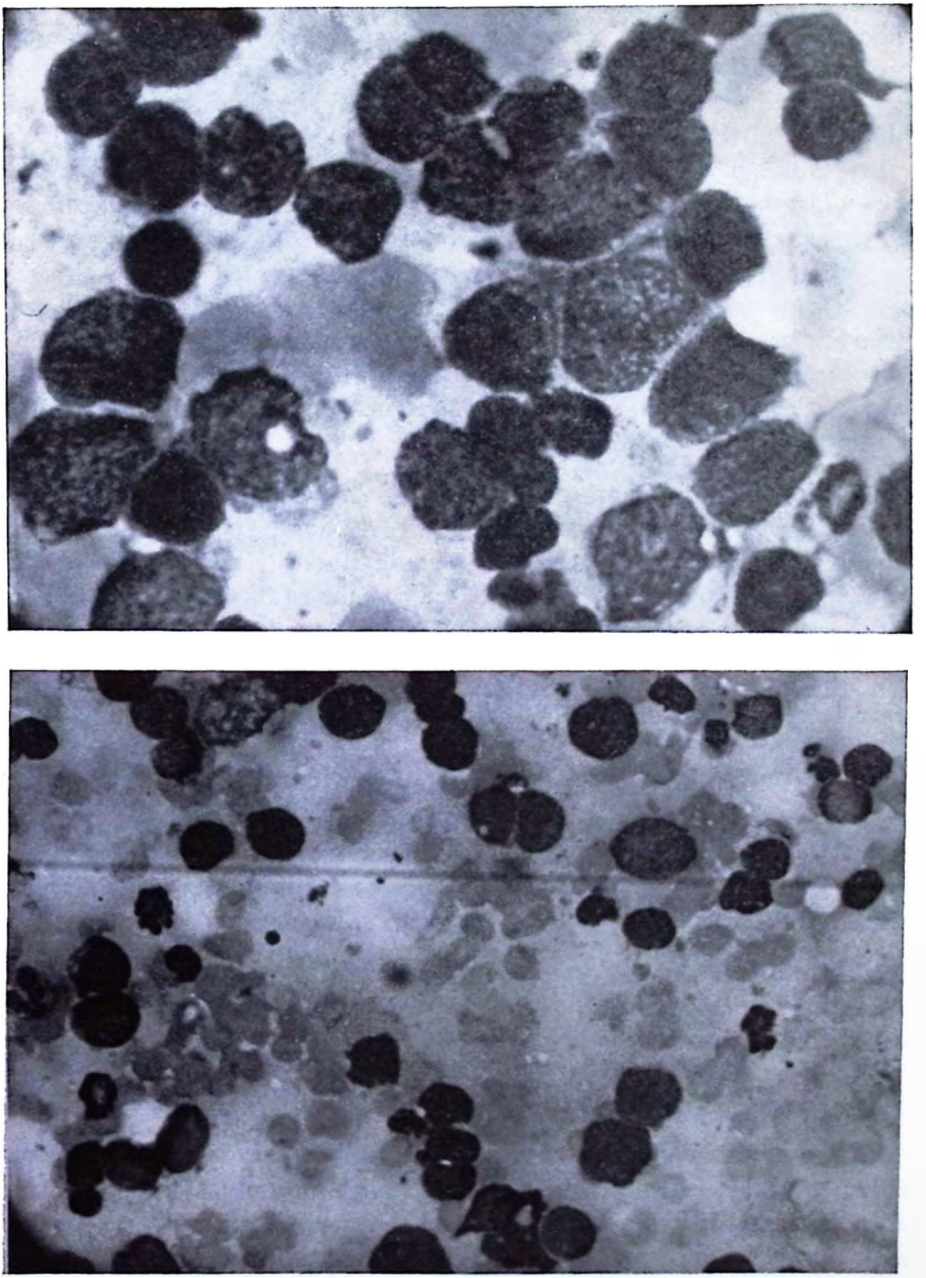

Figure 6-7
Bone marrow infiltration by retinoblastoma cells

Case IX, who had neonatal neuroblastoma, deserves some comment, since this form has been less frequently reported.[9] The patient was referred to this hospital because of skin lesions, abdominal distention and pallor. There was a large, hard, non-tender mass filling the entire right flank area, which was almost inseparable from the liver. The liver, itself, was enlarged, and more pronounced on the left. He had anemia with normoblasts and blast-like cells on the peripheral smear (Table II). Marrow infiltration has been reported in 9.7% of the patients with neonatal neuroblastoma.[9] In case IX the infiltration was complete replacement of the bone marrow. Intravenous pyelography showed displacement of the right kidney downward and to the left, but no calcification was seen. Bone survey was negative. Skin biopsy revealed the dignosis and he was given vincristine. The patient's course continued downhill and he died two weeks later. Permission for postmortem examination was not granted. Information about symptoms referrable to increased catecholamines during pregnancy[11] was unobtainable.

Retinoblastoma is an uncommon childhood solid tumor which frequently metastasizes in bone marrow.[2, 3] Although retinoblastoma cells resemble neuroblastoma cells, they generally are larger and contain granules in the cytoplasm (Figure 6, 7). Because of the diffuse infiltration of the marrow, anemia, and thrombocytopenia, it was first thought that this patient had acute myeloid leukemia; however, histologic examination proved the diagnosis to be retinoblastoma. This patient's bone survey was negative, which indicates that, similar to neuroblastoma, negative X-ray findings do not rule out the existence of bone marrow involvement.

We have insufficient evidence to conclude that the prognosis in patients with complete replacement of bone marrow by neuroblastoma differs from that of patients with scanty or no replacement, however, all of our patients died within a short time following diagnosis.

Since all of these cases were observed in 5 years (between 1966 and 1971), replacement of bone marrow by tumor cells does not appear to be as rare as reports indicate.

Summary

Complete replacement of bone marrow ,as observed in nine patients with neuroblastoma and in one patient with retinoblastoma. In three of the patients with neuroblastoma and the one with retinoblastoma, no bone changes were seen on X-rays. A considerable number of blast-like cells, normoblast and myelocytes were found in the peripheral smears of eight of these ten patients.

Acknowledgment

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