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Case Report

Bone Formation by Cancer Metastases

Case Report and Review of Literature

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Summary. The formation of heterotopic bone tissue in malignant tumors or in their metastases is extremely rare. In a 60 years old male patient with bronchogenic carcinoma (adenocarcinoma) extensive bone formation was observed within multiple metastases in the skeletal muscles. On the basis of the microscopic findings, the mechanism of bone formation by malignant tumors is discussed. Obviously, proliferation of local mesenchymal tissue and differentiation of mesenchymal cells to osteoblasts is induced by the tumor cells.

Zusammenfassung. Eine heterotope Knochenneubildung in malignen Tumoren oder deren Metastasen ist extrem selten. Bei einem 60jährigen Patienten zeigten multiple Muskelmetastasen eines Bronchialcarcinoms (Adenocarcinoms) eine ausgedehnte Verknöcherung. Auf Grund der histologischen Untersuchungsbefunde wird der Mechanismus der Knochenneubildung im Rahmen maligner Geschwülste diskutiert. Danach induzieren die Tumorzellen eine Proliferation des ortsständigen Mesenchyms mit Ausdifferenzierung der Mesenchymzellen zu Osteoblasten.

Although bone formation by malignant tumors, especially by mucigenous cancers of the gastrointestinal tract, is a rare event, several cases have been reported in the literature (Gruber, 1913, 1953; Hasegawa, 1923; McManus, 1966; Plenge 1955; further references see Plenge). However, ossification of metastases is extremely rare. The following case report deals with a patient with bronchogenic carcinoma in whom the first clinical symptoms were produced by multiple ossified metastases within the skeletal muscles. The mechanism of bone formation by tumor cells is discussed.

Case Report

60 years old male patient. Hypertension and fatty liver with development into liver cirrhosis known since 5 years. In January, 1975, the patient suffered from pain in the sacral region. In February the patient was hospitalized because a painless tumor had appeared in the soft tissues of the right thigh. At admission 8 nodes were observed in the soft tissues of the neck, the left dorsal thoracic wall, the left upper and forearm, the abdominal wall and the outside of both thighs. In addition subfebrile temperatures and cough were present. No hemoptysis. Neurological symptoms did not exist. On March 7, a node was excised from the muscles of the left thigh. It measured 6:3:3 cm and was of bony consistency.

Gratitude is expressed to Prof. Dominok (Cottbus) and Prof. Uehlinger (Zürich) for critical discussion of our case.

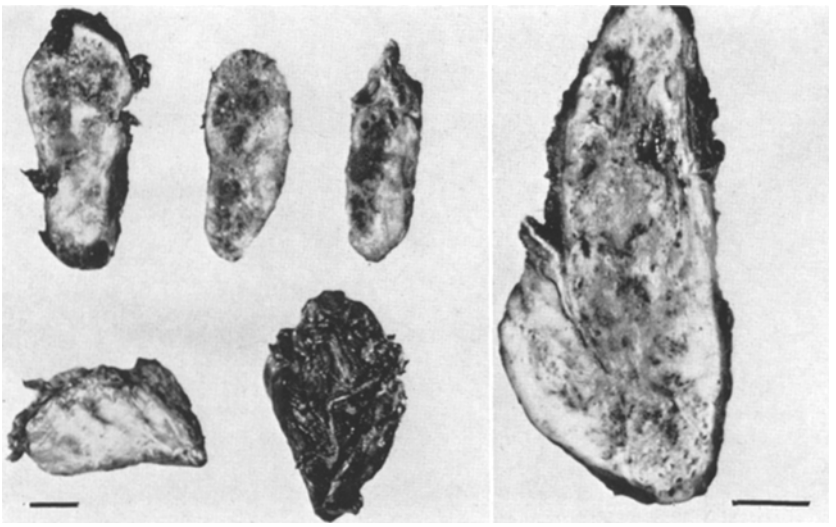

Fig. 1. Ossified cancer metastases in the skeletal muscles (after formalin fixation, surface and cut surface)

Microscopic Findings. Slim bony trabeculae in a reticular arrangement with a rim of osteoblasts on their surface. Between the trabeculae atypical glandular formations with marked cellular and nuclear polymorphism of the predominantly cuboid or cylindrical tumor cells which contain PAS negative secretory vacuoles. Loose fibrous stroma between the tumor glands. Marked increase of collagenous fibrous tissue with many fibroblasts in the periphery of the metastasis, in immediate neighborhood of atypical glands and destroyed muscle fibers. Differentiation of mesenchymal cells into osteoblasts with formation of bony ground substance and young bony trabeculae. Tumor tissue and newly formed osseous tissue were usually separated by cellular mesenchyme with osteoblasts.

Diagnosis. Muscle metastasis of an adenocarcinoma with heterotopic ossification.

Clinical Course. The following clinical examination failed to reveal a primary tumor. X-ray investigation demonstrated metastases in the spine and in the pelvic bones. Laboratory data: Alkaline phosphatase increased to 200 mU, acid phosphatase and electrolytes in the normal range. Electrophoresis: Increase of α_2-, β- and γ-globulins. 39 days after admission the patient developed high fever and expired under the symptoms of cardiac and circulatory insufficiency.

Autopsy Report. Bronchogenic carcinoma of the proximal part of the main bronchus to the left lower lobe; size 2.5:1.5:1.5 cm, with destruction of the bronchus wall. Multiple metastases (up to the size of a cherry) in the lymph nodes of the left pulmonary hilus, the tracheal bifurcation, in the paratracheal and paraortal lymph nodes and the lymph nodes of the mesenterial root. Hematogenous metastases in the liver, in both adrenals, in the second and fifth lumbar vertebral body, in both kidneys and in the thyroid gland. Numerous metastases of various size in the skeletal muscles: Smaller metastases (up to 3:1:1 cm) in the right abdominal wall, the seventh intercostal space and in the back of the neck above the spinous processes. Larger metastases (up to 6:3:3 cm) in both thighs and in the right calf. All the metastases had an oval shape with the long

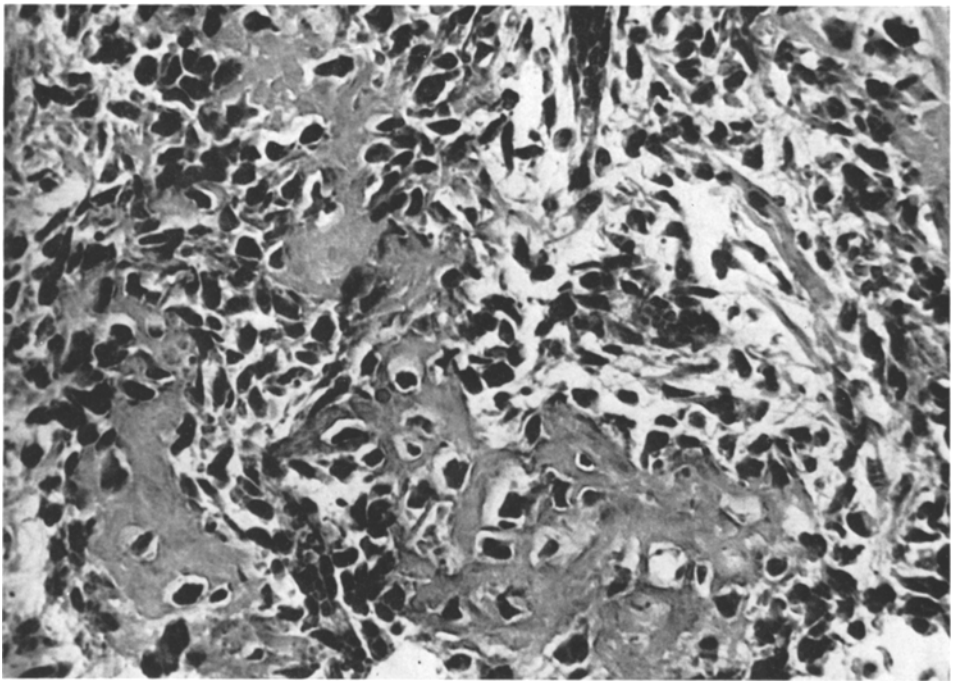

Fig. 2. Mesenchymal proliferation induced in the vicinity of a cancer metastasis in a skeletal muscle. Osteoid formation within the mesenchyme. Formalin. Paraplast. H.E., 680×

axis in the direction of the affected muscle. A small metastasis of a pea's size without bone formation was found in the M. thyreohyoideus.

In addition, the following organ changes were found: Nodular cirrhosis of the liver, splenomegaly, hypertrophy of the left heart (weight of the heart 510 g), ancient infarction of the cardiac septum (scar 4 : 4 cm), pulmonary edema.

Microscopically the pattern of the metastases within the skeletal muscles did not differ from that of the metastasis described above. Smaller metastases in the muscles and all the metastases in the inner organs did not show any bone formation. Also the heart demonstrated disseminated neoplastic infiltration, but no ossification was observed. Secretory activity was present in the tumor cells of all the metastases.

Discussion

The literature contains only few cases of heterotopic bone formation within cancer metastases (see Table 1), but ossification was markedly pronounced in the present case.

Different mechanisms of new bone formation by cancer cells have been discussed by former authors. The tumor cells are supposed to contain substances which may induce ossification (Laubmann, 1932; Micseh, 1933; Willis, 1952; Plenge, 1955; Gruber, 1953). According to Laubmann (1932) and Micseh (1933)

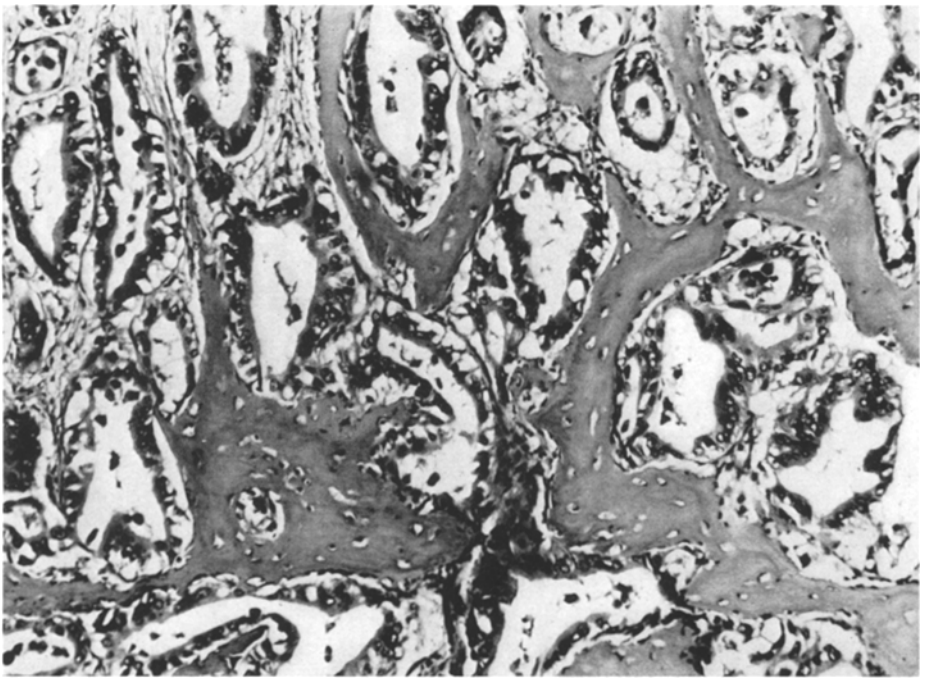

Fig. 3. Metastasis of the adenocarcinoma in a skeletal muscle. Secretory activity of tumor cells. Heterotopic bone formation. Formalin. Paraplast. H.E., 500×

the local mesenchyme is induced by the tumor cells to form bony tissue. Plenge (1955) considers that the cancer cells themselves may act as osteoblasts.

Metaplastic bone formation within connective tissue is well known (e.g. Letterer, 1959). This is true also for the interstitial tissue of the skeletal muscles (see Pendl, 1972; Adams *et al.*, 1967; Rüttner u. Koller, 1968) if muscle tissue is destroyed by trauma, inflammation or neoplastic infiltration.

The following conclusions in regard to the ossification of cancer metastases in muscle tissue are based on the microscopical findings in the present case:

1. Ossification occurred only in close anatomical relation to the cancer tissue. Since no bone formation was observed in other tissues outside the metastases, a hormonally induced paraneoplastic syndrome may be excluded. Also, the skeletal tissue outside the bone metastases did not show any increased bone destruction or bone formation.

2. Ossification was restricted to the metastases within the skeletal muscles and in the neighborhood of tendons and ligaments (Lig. nuchale). It was absent in the primary tumor and in the metastases within the lymph nodes and the inner organs. Therefore it is concluded that sufficient amounts of preexistent connective tissue and/or products of muscle degradation are needed by the tumor cells in order to induce bone formation. Bone formation within the primary tumor of Micseh's case (1933) was probably favored by the fact that the tumor (adenocarcinoma of the gall bladder) had developed in the presence of severe chronic

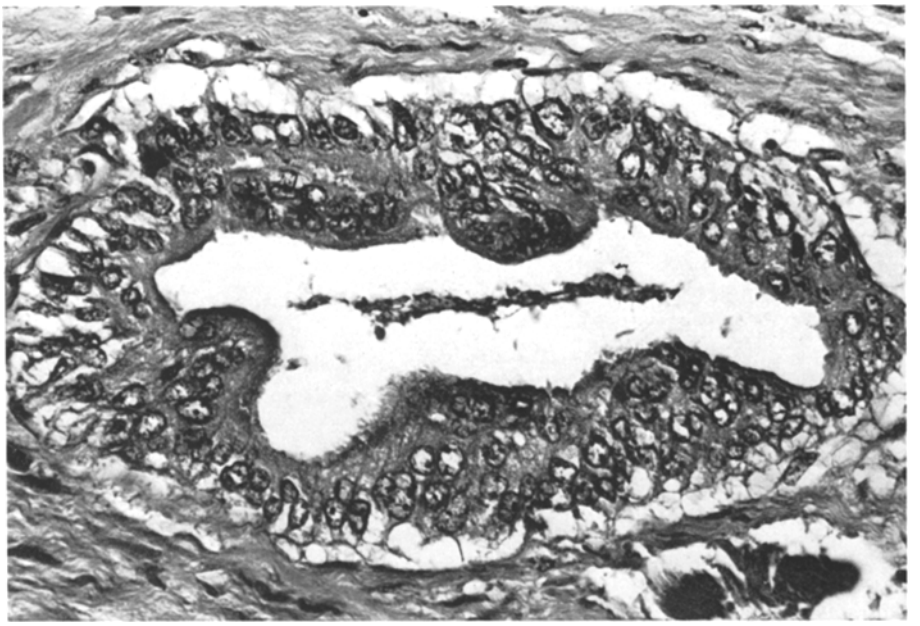

Fig. 4. Metastasis of the adenocarcinoma in a skeletal muscle. Secretory vacuoles in the epithelial cells of the atypical glands. Formalin. Paraplast. H.E., 1200×

Table 1. Heterotopic ossification of cancer metastases (review of literature)

Author	Sex	Age	Primary tumor	Localization of ossified metastases
Laubmann (1932)	M	65	Stomach Scirrhus	Lung
Micseh (1933)	F	55	Gallbladder Adenocarcinoma	Liver, lungs, lymph nodes
Plenge (1955)	F	59	Sigmoid-rectum Adenocarcinoma	Lung
Rüttner and Koller (1968)	F	63	Stomach Adenocarcinoma	Adductor muscles of both thighs
Dominok (personal communication) (1975)	M	56	Stomach Mucigenous adenocarcinoma	Regional lymph nodes
	M	74	Colon Mucigenous adenocarcinoma	Regional lymph nodes
	F	49	Breast Ca. solidum simplex	Dura
Present case (1975)	M	60	Bronchus Adenocarcinoma	Skeletal muscles, bone system

fibrosing cholecystitis. The distribution of the metastases in the present case does not confirm Plenge's (1955) opinion that the tumor cells themselves participate in bone formation.

3. A lack of active bone formation was observed in the center of the larger metastases and within the smaller metastases in the skeletal muscles. Apparently, the metastasis must have developed a critical size until bone formation occurs. Below that size the destruction of muscle tissue and/or the production of ossification-stimulating factors by the tumor cells (see below) may be insufficient to initiate bone formation. The lack of bone formation by the tumor cells in the myocardium may be due to mechanical factors in relation to permanent contraction of this muscle.

4. Secretory activity was demonstrated in the tumor cells of all the metastases (secretory vacuoles in the basal parts of the cells, occasionally mucigenous material in the lumina of the glands). It appears probable that the tumor cells discharge their secretion not only into the glandular spaces but (similar to the cells of a signet cell carcinoma) also into the surrounding tissues. If the secretory product contains substances which may induce mesenchymal proliferation and transformation of fibroblasts into osteoblasts, bone formation around the neoplastic glands may be the consequence. It is known that transplantation of urinary bladder mucosa into the abdominal wall of guinea pigs is followed by bone formation (Friedenstein, 1961) and that bone formation in this case is always accompanied by the secretion of glycogenlike polysaccharides from the transitional epithelium into the surrounding tissue. Autologous transplantation of gallbladder or gastric mucosa may produce ossification of muscle tissue within 2 to 3 weeks (Wojtek, 1964).

5. The ossification which is caused by cancer cells is independent from degenerative changes (especially necroses) of the tumor tissue. On the basis of our microscopic findings, a dystrophic calcification and ossification may be excluded.

6. The bone metastases in the present case were also characterized by new bone formation, but they did not show the extensive proliferation of mesenchymal tissue occurring within the muscle metastases. This may be explained by the fact that in the bone marrow no proliferation of mesenchymal cells and no transformation of these cells into osteoblasts must take place in order to induce the formation of new bone trabeculae. It is no longer supposed that inflammation around the metastatic tumor cells is responsible for the development of osteoplastic metastases (Lenzinger, 1886; Courvoisier, 1901; Schopper, 1939). Also, a direct rôle of the tumor cells in the production of new osseous tissue is denied today (Jaffé, 1958). Obviously, the formation of new bony material is caused by neoplastic bone destruction and thereby altered statics of the skeletal system (Assmann, 1907; Walther, 1955; Mc Manus, 1966). It is favored by the disturbed circulation in the vicinity of the metastases, e.g. by abnormal course of blood vessels, thrombosis, and ischemia (Schobinger, 1958; Dominok, 1971), similar to experimental ischemic bone reactions (Rutishauser *et al.*, 1960), formation of new lamellar systems in limbs with severely disturbed circulation (Lorrentz, 1960) and proliferation of connective and bone tissue in chronic congestive hyperemia (v. Recklinghausen, 1892). It is unknown whether circulatory alterations might have been an additional factor for the ossification in the muscle metastases of the present case.

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