

Copyright ©2002 Oxford University Press

Bulstrode, Christopher, Buckwalter, Joseph, Carr, Andrew, Marsh, Larry, Fairbank, Jeremy, Wilson-MacDonald, James, Bowden, Gavin

Oxford Textbook of Orthopedics & Trauma, 1st Edition

Pathology

Part of "3.19 - Pathologic fractures"

Pathogenesis of metastatic disease

There are two main theories that explain the pathogenesis of secondary tumors: the **blood distribution theory** and the **soil hypothesis theory**. These two theories may not be mutually exclusive. The blood distribution theory is dependent on the four major venous systems within the body: pulmonary, aortocaval, portal, and vertebral vein. The lung is the most common site of metastatic disease because the lung drains the systemic venous circulation and the main lymphatic trunks. The liver is drained by the portal venous system. Lung carcinoma can directly enter the pulmonary vein and metastasize via the heart to the peripheral organs. Hence, when there is a distant metastasis it may most commonly be from lung carcinoma. Batson's vertebral vein plexus contributes to tumor spread (Batson 1957). It is longitudinal and valveless, and runs from the sacrum to the base of the skull. The plexus connects the vertebrae, thorax, pelvis, brain, and proximal long bones to breast, lung, kidney, prostate, and thyroid. Tumor cells may move freely in Batson's plexus throughout body cavities.

The soil hypothesis theory, originally proposed by Paget in 1889, posits that the metastatic cells are distributed evenly over the body, but only certain organs provide the proper environment ('soil') for the growth of the neoplastic cell. It is increasingly obvious that local factors are important and that although metastatic cells may be filtered out by the capillary systems, their growth to produce a metastasis depends on a variety of factors. One of the most important variables is local growth factors. The metastatic cell must attach to

P.1767

the endothelium of a vessel wall before it can pass through. A large family of cell surface molecules called integrins play an important role in the process of attachment (Simon et al. 1994). The integrins are thought to be important in the transport of cells through the basement membrane of normal vessels. The integrins seem to act as facilitators to the passage of cells. A possible explanation for the site-specific nature of metastasis may be that the neoplastic cell integrin must be specific. It is known that some types of metastasizing cells produce type IV collagenase. Type IV collagen is the predominant type of collagen in the basement membrane. Angiogenesis must also occur for a metastatic focus to become a clinically important metastasis. Angiogenesis in some tumors is driven by tumor angiogenesis factor. Tumor angiogenesis factor is probably excreted by neoplastic cells.

Box 2 Incidence and prevalence of pathologic fractures

- Bimodal age prevention
- 1.2 million new cancer cases in the United States
- 60 per cent of these with breast, prostate, lung, kidney, or thyroid tumors
- Bone is the third most common site of metastasis
- Breast and prostate comprise 90 per cent bone metastases found at autopsy
- Sites of red blood cell production most common

Box 3 Pathogenesis of metastatic disease

- Blood distribution theory
- Soil hypothesis theory

Pathophysiology of metastatic disease

The pathophysiology of metastatic bone disease is complex. The behavior of metastatic cells can be indolent, only slowly react, or may rapidly destroy the structure of bone. The host bone may have little or no response or may become profoundly osteoblastic. A radiograph may show a mixed pattern of bone destruction (Fig. 1) or it may

P.1768

be purely lytic (Fig. 2) or purely blastic (Fig. 3). It is a common misconception that the metastatic cells destroy the bone. Bone destruction is secondary to osteoclastic activity being activated by the metastatic disease. New bone formation seen in metastasis can be reactive bone or stromal bone. Stromal bone has a fibrous background and is common in breast or prostate carcinoma.

Fig. 1. Metastatic lesions in the left hemipelvis and proximal femur from a 62-year-old female with breast carcinoma. The patient was unfit for surgical salvage procedure and was treated with analgesia, radiotherapy, and hormonal modulation.

Fig. 2. Metastatic renal lytic lesion in the femoral shaft of the femur in a 40-year-old male. The femur was stabilized with a locked cephalomedullary intramedullary nail.

Fig. 3. Metastatic osteoblastic prostatic fracture in the right proximal femur in a 69-year-old male. The femur was stabilized with a locked cephalomedullary intramedullary nail.

Box 4 Abnormalities associated with pathologic fractures

- Hematologic abnormalities:
 - normocytic hemochromic anemia
 - raised white cell count or low neutrophil count
 - thrombocytopenia common
- Biochemical abnormalities:
 - raised serum calcium
 - look for polyuria, polydipsia, anorexia, fatigueability and weakness
 - in chronic hypercalcemia look for drowsiness, coma, nausea/vomiting, pruritis, etc.

Associated pathology

Hypercalcemia may occur in metastatic bone tumors or in hyperparathyroidism and can be a difficult problem to treat. If the serum calcium level rises slowly, the patient may be asymptomatic. If the rise is fast, there may be signs of hypercalcemia with polyuria, polydipsia, anorexia, easy fatiguability, drowsiness, and weakness. A slow rise in serum calcium may give more subtle clinical signs. Untreated hypercalcemia may lead to drowsiness with progression to coma, associated with nausea, vomiting, pruritus, visual abnormalities, profound muscle weakness, and abdominal pain. Treatment is with oral hydration, intravenous saline diuresis, and intravenous pamidronate.

Most patients with metastatic disease will have a normocytic normochromic anemia secondary to bone marrow replacement or radiotherapy and chemotherapy. Many patients will have an elevated white blood cell count and a leukoerythroblastic shift. Patients may require correction of anemia and thrombocytopenia before surgery. Very low neutrophil counts may preclude surgery because of the risk of overwhelming sepsis.