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BONE MARROW EVALUATION IN SMALL CELL CARCINOMA OF THE LUNG

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Abstract

Bone marrow examination is commonly included in the staging of small cell lung carcinoma (SCLC). We reviewed marrow samples of 103 patients. Marrow examination was mainly performed by unilateral or bilateral biopsy of iliac crests, using a Jamshidi needle. Only 6 of 97 evaluable cases (6.2 per cent) were positive for marrow metastases at staging, and in 3 cases (3 per cent) bone marrow was the only metastatic site. No focal metastases were found in additional sections made from the blocks of negative samples. In our experience bone marrow biopsy was of little value in staging SCLC. Bilateral biopsy plus aspirate, with the addition of more sophisticated staining techniques might, however, provide a higher yield of positive marrow involvement.

Key words: Lung neoplasms; small cell carcinoma, bone marrow biopsy.

Despite aggressive polychemotherapy, long survival is unusual in small cell lung carcinoma (SCLC) patients with extensive disease (1).

An increasing number of diagnostic methods has been used for staging of SCLC and has improved the precision of the staging. Metastases of SCLC frequently involve liver, central nervous system, bone and adrenals, and intrathoracic, supraclavicular and infradiaphragmatic lymph nodes (27).

The incidence of bone marrow metastases varies widely between 15 and 50 per cent, according to different reported series. Bone marrow involvement can be detected by means of radionuclide scanning, bone radiography and histologic or cytologic bone marrow examination. It may also be suggested by thrombocytopenia or leukoerythroblastic peripheral blood smears (15). Radionuclide scanning can diagnose bone metastases earlier than radiography (26). Bone marrow for histologic examination can be obtained by biopsy of the postero-superior iliac crests, and bone marrow aspirates for cytology from the same site, or from manubrium sterni.

It has been reported that bilateral iliac crest biopsy is superior to the unilateral procedure and that bone marrow aspirate can give some additional information (3, 16, 17). These findings, however, have not been confirmed by other authors (21, 22). Bone marrow examination and bone radionuclide scanning seem to be complementary investigations (20, 23, 24), since they can detect different patterns of metastatic involvement.

Bone marrow evaluation is a rather uncomfortable and expensive procedure and may, in addition, delay treatment and prolong the hospital stay. We therefore reviewed the bone marrow samples obtained at our department in order to evaluate the necessity and utility of this technique.

Material and Methods

Bone marrow samples of 103 patients with cytologic or histologic diagnosis of SCLC, referred for treatment to our institution between January 1982 and March 1985, were reviewed. Patient characteristics are summarized in the Table. There were 54 patients with limited disease (disease confined to one hemithorax, including ipsilateral supraclavicular, hilar and mediastinal lymph nodes and pleura) and 43 with extensive disease. In 6 patients the biopsies were inadequate.

Staging included in all patients complete blood and platelet counts, 12-channel blood profile, liver function tests, chest radiography plus tomography, radionuclide scan of bones, ultrasound or CT scan of liver and adrenals, and brain CT scan.

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The bone marrow was evaluated by sternal aspirate alone in 2 cases. In all the other patients unilateral or bilateral bone biopsy was obtained from the postero-superior iliac crests by a Jamshidi needle. In two patients both bilateral biopsies and marrow aspirates were examined.

The marrow aspirates were stained according to the May-Grünwald-Giemsa technique. The bone samples were processed according to BUSSOLATI (5), with simultaneous fixation and decalcification. By this method fixation and decalcification are complete in 24 h, with excellent morphologic characteristics and nuclear staining. The final paraffin specimens were sectioned (6 consecutive sections, 5 μm in thickness) and routinely stained with hematoxylin-eosin and Giemsa.

Given the low yield of positive findings in our series, we made additional histologic sections (one section 4 μm in thickness for every 100 μm of the total embedded block) from the biopsies which were negative at first examination. Reexaminiation of these cases was motivated by the reported focal involvement with discovery of small nests of tumor cells in serial sections only (6, 19, 29). Only specimens with an adequate length (totally >2 cm) including a minimum of cortical bone or blood clot were reexamined. Thus 56 of 91 negative cases were reevaluated.

Bone scanning was started 2 to 5 h after injection of 555 MBq $^{99}Tc^{m}$ methylene diphosphonate. Patients whose scans showed areas of increased deposition were examined by radiography and, when focal areas of increased uptake could not be attributed to benign disorders (as arthritis, Paget's disease, trauma, infection), a scan was considered positive for malignancy.

Results

A total of 158 biopsies and 4 aspirates were examined in 103 different patients with SCLC. In six patients the samples were considered inadequate. In 2 of the 97 evaluable cases marrow aspirates only were examined, while 53 and 48 patients had unilateral or bilateral bone biopsy respectively. Two patients had bilateral biopsy plus bone marrow aspirate. Mean length of each biopsy was 1.65 cm (median 1.6 cm; range 0.2–4 cm) with a diameter of 0.2 to 0.3 cm. All 4 bone marrow aspirates were negative. Overall, the bone marrow examination showed tumor cells in only 6 of the 97 evaluable patients (6.2 per cent), all males. Three of these patients were staged as extensive disease cases due to the bone marrow findings alone (7 per cent of 43); the other 3 patients had metastases in bone confirmed at radiography. In 4 positive cases the biopsy was bilateral; in all cases, however, a metastasis was found on one side only. No hematologic abnormalities were observed at diagnosis in any patient. Bone radiographs were negative in 3 cases. All these cases had, however, radionuclide scans suspicious for bone metastases. Of the 91 negative cases 56 were reevaluated after further cutting of the original blocks. No additional microfoci of metastasis were discovered in the new sections.

Table
Patient characteristics

Total number of patients	103
Sex (male/female)	90/13
Median age (range)	59 (32–73)
Patients with evaluable bone marrow	97
Limited disease	54 (56%)
Extensive disease	43 (44%)
Patients with single site of distant metastasis	26
Liver	11
Lung	2
Lymph nodes	2
Bone	3
CNS	3
Chest wall	1
Skin	1
Bone marrow	3

Discussion

The overall incidence of bone marrow involvement in SCLC has in some clinical series been reported to be between 15 and 50 per cent (14, 25), while in autopsy series frequencies of 35 to 55 per cent have been found (19). In more recent clinical series, however, a lower incidence of marrow metastases at diagnosis has been reported, with a mean of about 25 per cent (8, 13, 16, 18, 21–23). Bilateral biopsy has been stated to increase the yield of positive marrow evaluation by 11 to 30 per cent over the unilateral procedure (3, 17). According to HIRSCH et coll. (16) bone marrow aspirate gives a higher yield than biopsy, and biopsy and aspirate seem to give complementary information (10, 12, 16, 29). However, some recent reports state that an adequate bone biopsy is nearly equivalent to the combined procedure (21–23). In conflict with the findings of HIRSCH et coll. is the fact that marrow invasion by SCLC stimulates osteoblastic and myelofibrotic processes which often cause dry taps (19).

In our series we found an incidence of marrow involvement of 6.2 per cent, which is one of the lowest figures reported in the literature. There was a predominance of patients with limited disease in our series, due to the nature of the early trials at our department. However, the difference in this respect between our material and other reported series was small and unlikely to be entirely responsible for our low yield of positive bone marrow samples. The median length of bone biopsies in our series was inferior to that reported by LAWRENCE et coll. (22), who used a similar Jamshidi needle. Other authors (9, 16), however, obtained 17.2 per cent positivity utilizing the Radner needle, that makes biopsies of 1 cm only.

Bone evaluation by radionuclide scanning is subject of a

renewed interest. There are, however, unfortunately no universally accepted criteria for this evaluation (7). A lack of correlation between radionuclide scanning and bone marrow examination has been supposed and both procedures have been recommended for staging of SCLC (20, 23, 24). LEVITAN et coll. (23), found as the only sign of an extensive disease, a positive bone marrow biopsy in 8 per cent of 112 patients with negative bone scans. In an additional 9 per cent both biopsy and scans were positive.

In our series we did not find any positive bone marrow in absence of a suspicious or positive bone scan; in 3 of the cases with positive bone marrow radiography showed bone metastases.

In conclusion, our series showed an unexpectedly low frequency of bone marrow metastases, revealed by unilateral or bilateral iliac crest biopsy. In the way we performed the examination bone marrow biopsy was of little value in initial staging of SCLC, in agreement with some other reports (13, 18, 19). In our opinion bone biopsy should be performed in all cases where bone scan is suspicious. It has been suggested that high levels of serum LDH correlate with bone marrow metastases and that bone marrow biopsy could be superfluous as a routine staging procedure (28). The use of bone marrow aspirate in combination with bilateral biopsy might be considered in order to increase the yield of positive findings. More sophisticated staining techniques (e.g. monoclonal antibodies) will probably improve the detection of bone marrow microfoci.

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