Hypertrophic Pulmonary Osteoarthropathy*

John H. Stenseth, M.D., O. Theron Clagett, M.D., F.C.C.P.,
Lewis B. Woolner, M.D.

Rochester, Minnesota

Clubbing of the digits has been known to exist since antiquity, having been described first by Hippocrates' in the fifth century B.C. However, the recognition that the association of clubbing, arthralgia, and ossifying periostitis of the long bones represents a distinct clinical entity must properly be credited to Bamberger5 and Marie6 in 1889 and 1890. Prior to that time, the occurrence of this triad, which is now referred to as "hypertrophic pulmonary osteoarthropathy," had been noted by numerous clinicians and investigators, but it was always thought to represent a variant of the clinical spectrum of acromegaly. Typical of the descriptions of this era, Saunby,4 in 1889, described a patient with "thickening of the hands and joints" who was found at necropsy to have "a sarcoma of the left lung." Saunby concluded that this patient was acromegalic and that the association of the findings in the limb and the tumor "could only be coincidental."

Bamberger's5 description of two patients with bronchiectasis and associated pulmonary osteoarthropathy and Marie's6 description of four patients with various chest conditions and associated osteoarthropathy focused attention on the thorax as the site of the primary pathologic condition in patients with the symptom complex of clubbing of the digits, arthralgia, and ossifying periostitis of the long bones. Thompson,8 in 1904, was the first to note the association of pulmonary osteoarthropathy and bronchogenic carcinoma. Since that time, Mendlowitz2 and others3,4 have pointed out that hypertrophic pulmonary osteoarthropathy has been noted in association with a wide variety of intrathoracic pathologic states, including both pulmonary and cardiovascular lesions. Some of these pathologic entities include benign and malignant neoplasms of the lung, mediastinum, and pleura; pulmonary tuberculosis; pneumoconioses; pulmonary hemangiomias and congenital pulmonary cysts; empyema; atelectasis; cyanotic congenital heart lesions; subacute bacterial endocarditis; aneurysms of the arch of the aorta or its major branches; and neoplasms metastatic to the lung or thoracic structures. Hypertrophic pulmonary osteoarthropathy has also been noted in association with chronic methemoglobinemia and sulfhemoglobinemia,8 with polycythemia as a result of living for prolonged periods at high altitudes;14 with cholangiolic biliary cirrhosis,6 amyloidosis of the liver, and liver abscess;15 and with chronic ulcerative colitis, regional enteritis, and multiple polyposis.6 Clubbing of digits may also occur without the joint symptoms characteristic of hypertrophic pulmonary osteoarthropathy. In this regard it is more properly referred to as pachydermoperiostosis and, when associated with marked thickening of the skin of the face and forehead, represents an idiopathic hereditary condition known as the Touraine-Solente-Golé syndrome.11

Despite this diversity of disease conditions with which hypertrophic pulmonary osteoarthropathy has been seen to coexist, in practice, the association of this characteristic symptom complex with bronchogenic carcinoma must be the primary consideration and concern; at present, bronchogenic carcinoma is regarded as the major cause of osteoarthropathy.10-13

*From the Mayo Clinic and Mayo Foundation: Section of Surgery (Dr. Clagett) and of Surgical Pathology (Dr. Woolner). Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Surgery (Dr. Stenseth).
This paper reviews in detail the association of hypertrophic pulmonary osteoarthropathy and tumors of the lung in regard to incidence, cell type, significance relative to the presence or absence of metastasis from the primary site, and incidence of occurrence as the only manifestation of an intrapulmonary pathologic condition. It also reviews various theories concerning the cause of hypertrophic pulmonary osteoarthropathy and attempts to correlate the findings of this study with an accepted etiologic theory.

METHOD

The records were reviewed of all patients who, during the period 1953 through 1962, underwent thoracotomy at the Mayo Clinic for treatment of known bronchogenic carcinoma, for confirmation of the diagnosis of presumptive bronchogenic carcinoma, for excision of a presumed metastatic lesion in the lung, or for determination of the nature of an unknown lesion in the lung.

Information concerning the age and sex of the patient, the presence or absence of associated pulmonary osteoarthropathy, the type and effect of procedure done, the type of tumor found (including its cell type, grade, size, and location), the results of various laboratory and other diagnostic procedures, the presence or absence of metastasis, and the ultimate outcome regarding survival was recorded in each case.

All cases of mesothelioma were excluded from the study because previous papers from this institution have already dealt with that interesting tumor and its relationship to hypertrophic pulmonary osteoarthropathy in some detail.

RESULTS

During the ten-year period studied, 1,879 patients underwent 1,888 thoracotomies for lung lesions at the Mayo Clinic (nine patients underwent two thoracotomies each during this period and each operation is considered as a separate case). Of these, 174 cases (9.2 per cent) included associated hypertrophic pulmonary osteoarthropathy. As noted in Table 1, both primary and metastatic tumors of the lung may be associated with osteoarthropathy. Of the seven cases of metastatic disease with associated osteoarthropathy, the primary sites were in the breast in two, unknown in two, and in the uterus, prostate, and right upper arm in one each. With the exception of the fibrosarcoma metastatic from the right upper arm, all of these metastatic cases were adenocarcinoma.

Table 2 presents an analysis of the 1,657 cases of primary pulmonary tumors according to cell type, relative incidence of each type, and number of cases with associated hypertrophic pulmonary osteoarthropathy according to cell type. Of the cases of primary bronchogenic adenocarcinoma, 22 (1.3 per cent) were of the alveolar cell type, and one of these 22 cases exhibited hypertrophic pulmonary osteoarthropathy. There were 66 bronchial adenomas; 51 (3.1 per cent) were carcinoid type, 11 (0.7 per cent) were unclassified, and 4 (0.2 per cent) were cylindroma. Of these bronchial adenomas, one case each of the carcinoid and unclassified groups had associated osteoarthropathy.

Fourteen tumors were of mixed cell type: eight squamous adenocarcinomas, and six carcinosarcomas. None of the tumors in this group exhibited associated osteoarthropathy. Of particular interest to us was the finding that 5 per cent of the small cell carcinomas had associated pulmonary osteoarthropathy, since Yacoub recently report-
STENSETH, CLAGETT AND WOOLNER

TABLE 2—INCIDENCE OF HYPERTROPHIC PULMONARY OSTEARTHROPATHY (HPO) ACCORDING TO CELL TYPE WITH PRIMARY LUNG TUMORS

<table>
<thead>
<tr>
<th>Cell type</th>
<th>No. cases</th>
<th>% of total</th>
<th>No. with HPO</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous carcinoma</td>
<td>357</td>
<td>21.5</td>
<td>92</td>
<td>11.8</td>
</tr>
<tr>
<td>Large cell</td>
<td>66</td>
<td>4.0</td>
<td>3</td>
<td>3.0</td>
</tr>
<tr>
<td>Small cell</td>
<td>267</td>
<td>16.1</td>
<td>84</td>
<td>14.2</td>
</tr>
<tr>
<td>Bronchial adenoma</td>
<td>139</td>
<td>8.4</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>26</td>
<td>1.6</td>
<td>7</td>
<td>7.7</td>
</tr>
<tr>
<td>Mixed</td>
<td>14</td>
<td>0.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>84</td>
<td>5.1</td>
<td>7</td>
<td>8.3</td>
</tr>
<tr>
<td>Total</td>
<td>1,657</td>
<td>100.0</td>
<td>167</td>
<td>10.1</td>
</tr>
</tbody>
</table>

group, the reverse situation was found to exist.

The two groups were also compared on a basis of tumor location, grade, and spread to other structures. In 51 per cent of the primary cases and 84 per cent of the metastatic cases in the group without associated osteoarthropathy, the tumors were located laterally (that is, in or beyond a bronchus peripheral to the primary lobar bronchi). Similarly, in 66 per cent of the primary and 86 per cent of the metastatic cases in the group with associated osteoarthropathy, the tumors arose laterally. Seventy-seven per cent of all tumors without associated pulmonary osteoarthropathy and 91 per cent of all tumors with associated osteoarthropathy were either grade 3 or 4 (Broders’ classification). Comparison of the two groups on the basis of frequency of involvement of the visceral or parietal pleura, chest wall, mediastinum, and regional, hilar, or mediastinal lymph nodes showed almost exact similarity between the two groups.

Table 4 shows the mean survival times for both groups of patients. The follow-up period varied from three to 12 years; 39 patients were lost to follow-up, yielding a follow-up of 97.9 per cent. At the time of the study, 1,351 patients (71.9 per cent) had died and 489 patients (26.0 per cent) were still living. Among those patients who had pulmonary osteoarthropathy, four were lost to follow-up (97.7 per cent follow-up), 119 (68.4 per cent) had died at the time of the study, and 51 (29.3 per cent) were still living. Table 4 shows that the survival time was approximately equal for the groups of patients with primary bronchogenic carcinoma but,

<table>
<thead>
<tr>
<th>Patients</th>
<th>Mean age (yr)</th>
<th>Tumor size (cm³)</th>
<th>Mean age (yr)</th>
<th>Tumor size (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Tumor size</td>
<td>Men</td>
</tr>
<tr>
<td>With HPO</td>
<td>58.8</td>
<td>56.5</td>
<td>189.1</td>
<td>59.0</td>
</tr>
<tr>
<td>Without HPO</td>
<td>55.8</td>
<td>53.3</td>
<td>92.4</td>
<td>53.2</td>
</tr>
</tbody>
</table>

The results of this study were in agreement with the well-established fact that bronchogenic carcinoma is predominantly a disease of men: the men-to-women ratio for the total study was 3.96:1. In those cases without associated hypertrophic pulmonary osteoarthropathy, the men-to-women ratio was 3.86:1 and in those cases with associated osteoarthropathy it was 5.37:1. Table 3 shows the mean ages of all patients in both the primary and metastatic tumor groups. The patients with hypertrophic pulmonary osteoarthropathy tended to be slightly older, on the average, than those without osteoarthropathy, but the differences are not significant.

Table 3 also shows the mean tumor sizes. In the primary tumor group, the tumors associated with osteoarthropathy were about twice as large, on the average, as those not associated with osteoarthropathy. In the metastatic tumor group, the reverse situation was found to exist.

ed that he found no association between this cell type and osteoarthropathy.

Diseases of the Chest
for those patients with tumors metastatic to the lung, the group without associated hypertrophic pulmonary osteoarthropathy survived approximately twice as long as did those with osteoarthropathy.

Comparison of the two groups of patients in terms of erythrocyte sedimentation rate, abnormalities on thoracic roentgenograms, findings at bronchoscopy, and the number and type of associated pulmonary symptoms (cough, hemoptysis, dyspnea, chest pain, wheezing, hoarseness) failed to reveal any significant differences.

Of the total group of 1,888 cases, 471 (25.0 per cent) were found to be inoperable at exploration. Of the 1,714 cases without associated osteoarthropathy, 429 (25.0 per cent) were inoperable; 42 (24.1 per cent) of the 174 cases with associated osteoarthropathy were inoperable.

Among those patients with associated pulmonary osteoarthropathy, the onset of the typical signs and symptoms of osteoarthropathy coincided with the onset of pulmonary symptoms in 32.5 per cent of the cases. It preceded the onset of pulmonary symptoms in 30.0 per cent of the cases, generally appearing one to three months before pulmonary manifestations appeared. In 37.5 per cent of the cases, the manifestations of osteoarthropathy followed the appearance of pulmonary symptoms, again generally by one to three months. In 16 (9.2 per cent) cases the symptoms of hypertrophic pulmonary osteoarthropathy were the only manifestation of a pulmonary tumor, and in each of these cases the tumor was a primary bronchogenic carcinoma.

Information relating to the regression of the manifestations of osteoarthropathy was available in approximately 20 per cent of the cases. The arthralgia accompanying the other manifestations of osteoarthropathy disappeared immediately postoperatively in 36.8 per cent of these cases, by the end of the first week in 73.6 per cent, and by the end of the first month in 84.2 per cent. In the remainder of the cases, up to six months was required for the arthralgia to disappear completely. Clubbing regressed much more slowly, generally requiring three to eight months before satisfactory regression was evident. In one case, the manifestations of clubbing showed definite improvement but were still present five years postoperatively.

The type of operative procedure performed appeared to have no bearing on the regression of the manifestations of osteoarthropathy. In 36.8 per cent of the operable cases pneumonectomy had been performed, while in 63.2 per cent a lesser resection (lobectomy or segmental resection) had been necessary. In one case, in which only an exploratory thoracotomy was performed, the arthralgia disappeared completely six months postoperatively, although clubbing was still present and unchanged four years later (at the time of this patient's death).

**Discussion and Conclusions**

On the basis of our data, several conclusions may be reached concerning the relationship between hypertrophic pulmonary osteoarthropathy and pulmonary neoplasms. Osteoarthropathy clearly occurs with primary neoplasms of the lung, both malignant and benign, as well as with lesions metastatic to the lung. The incidence of its occurrence with primary tumors was approximately 10 per cent but with metastatic tumors it was only 3 per cent.

<table>
<thead>
<tr>
<th>Table 4—Mean Survival Time of Patients with Primary and Metastatic Tumors of the Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival (months)</td>
</tr>
<tr>
<td>Patients</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Dead</td>
</tr>
<tr>
<td>Living</td>
</tr>
</tbody>
</table>
Osteoarthropathy was noted with every cell type of bronchogenic carcinoma, the incidence varying from 10 to 15 per cent except for an incidence of 5 per cent in association with small cell carcinoma. However, although osteoarthropathy apparently occurs less frequently with this last cell type, our study fails to confirm the impression of Yacoub that osteoarthropathy never occurs in association with small cell ("coat cell") carcinoma.

In the majority (approximately 70 per cent) of cases of primary bronchogenic neoplasms with associated osteoarthropathy, the lesion was found to be peripheral to the primary lobar bronchi. This is in contrast to those cases without evidence of osteoarthropathy, in which only 50 per cent of the lesions were found in the more peripheral parts of the lung. However, further comparison of the two groups in relation to pleural involvement, chest wall or mediastinal invasion, or frequency of lymph node involvement revealed no significant differences.

The significance of the reversal of the tumor-size relationship in the primary tumor groups with and without osteoarthropathy and in the metastatic tumor groups is not at all clear. However, even though the primary tumors in the patients with osteoarthropathy tended, on the average, to be more than twice as large as the tumors in those without osteoarthropathy, the incidences of inoperability in these two groups were almost identical.

Prognostically, the association of hypertrophic pulmonary osteoarthropathy with primary bronchogenic neoplasms seems to be of no significance. However, the appearance of osteoarthropathy in a patient with a lung lesion metastatic from a distant site carries rather grave prognostic significance because the patients in this category died of their disease approximately twice as rapidly as those patients having metastatic tumors without associated osteoarthropathy.

**Etiology**—The cause of hypertrophic pulmonary osteoarthropathy has remained an elusive and perplexing problem ever since Marie first proposed that the characteristic findings in this condition resulted from a selective absorption of toxins from the affected lung. Numerous investigators since have proposed other theories to explain the appearance of osteoarthropathy, but no one has been able to offer irrefutable proof of any of these theories. Fried and Bloom concluded that osteoarthropathy reflects the result of "dyspulituitarism" in the affected patients. Mendowitz and Leslie and others thought that osteoarthropathy is a manifestation of chronic arterial anoxemia. More recently, a number of seemingly unrelated discoveries have led to the synthesis of another theory.

In 1953, Cudkowicz and Armstrong utilized a postmortem injection technique to demonstrate bronchial artery-pulmonary artery anastomoses in the immediate vicinity of malignant pulmonary neoplasms and found associated hyperplasia of the walls and narrowing of the lumina of the bronchial arteries distal to the site of these anastomoses, suggestive of spasm and decreased function. These changes were present only in the lungs of patients with associated osteoarthropathy; they were absent in the lungs of patients with no pulmonary disease and in the lungs of patients with malignant pulmonary neoplasms without associated osteoarthropathy. Semple and McCluskie concluded that these changes caused ischemia of the peripheral nerve fibers of the lung, which, in turn, reflexly influenced the formation of the systemic arteriovenous anastomoses in the lung that have been described as being present in and responsible for the manifestations of hypertrophic osteoarthropathy.

Holling and his associates confirmed this impression in 1961 when they discovered that bilateral cervical vagotomy caused a prompt reduction in blood flow in an extremity with a subsequent regression of the vascular connective tissue overgrowth which generally preceded the periosteal bony changes characteristic of hy-
pertrophic pulmonary osteoarthropathy in dogs. They further discovered that atropinization of the animals, which selectively inhibits vagal motor fibers, did not have this same effect. They therefore concluded that vagotomy was effective through interruption of afferent fibers. They were unable to find the efferent limb of the reflex. One year later, Diner' reported relief of the symptoms of osteoarthropathy after intrathoracic vagotomy in a patient with a lymphoepithelioma of the nasopharynx metastatic to the lung. Others, including ourselves, have had occasion to observe this same regression of symptoms after vagotomy in cases of primary as well as metastatic lung neoplasms.

We think that our clinical observation of the remission of the symptoms of hypertrophic pulmonary osteoarthropathy after simple vagotomy on the side of an inoperable lesion plus the results of this study in which the features of osteoarthropathy were seen to regress after pneumonectomy (in which we routinely sacrifice the vagus nerve) and also after a lesser resection (in which the vagal fibers to the area of the tumor are interrupted) tend to support this theory.

Thus, the afferent limb of this reflex apparently arises from nerve impulses originating in or near the neoplasm and travels to the central nervous system by way of the vagus nerve. Presumably, these impulses would then be mediated by the hypothalamus to cause secretion of some substance from the pituitary which in turn is responsible for the changes seen in hypertrophic pulmonary osteoarthropathy. The evidence for the character of the efferent limb of this proposed reflex is scanty and, to date, is principally indirect in nature. Semple and McCluskie' reported the excretion of “an unidentified substance... lethal to laboratory mice” in the urine of patients with osteoarthropathy. Berman' and others' have noted the frequent association of bronchogenic carcinoma, osteoarthropathy, and gynecomastia. Ginsburg and Brown' found that the excretion of estrogen in a group of patients with bronchogenic carcinoma and osteoarthropathy was nearly twice that in healthy controls or in patients with bronchogenic carcinoma without associated osteoarthropathy. While this evidence certainly does not identify a specific substance secreted by the pituitary as responsible for the manifestations of osteoarthropathy, it does at least suggest some degree of increased pituitary activity in patients with osteoarthropathy and, in this respect, it does tend to add support to the neurogenic theory.

The question arises why one tumor should have associated hypertrophic pulmonary osteoarthropathy while a similar tumor of identical cell type in another patient does not. Similarly, it is equally difficult to account for the regression of the manifestations of osteoarthropathy after simple exploratory thoracotomy, as seen in one case in this series, on the basis of the neurogenic theory. Also, it is rather difficult to make use of this theory to explain the appearance of osteoarthropathy with other widely divergent pathologic states such as aneurysm of the arch of the aorta, cholangiolitic biliary cirrhosis and chronic methemoglobinemia.

**Summary**

The records of 1,888 cases of pulmonary neoplasm operated on at the Mayo Clinic between 1953 and 1963 were reviewed. The incidence of hypertrophic pulmonary osteoarthropathy for the total group of cases, including both benign and malignant primary lung tumors as well as tumors metastatic to the lung, was 9.2 per cent. Hypertrophic pulmonary osteoarthropathy was associated with all cell types of primary bronchogenic carcinoma except the cylindromic form of bronchial adenoma and mixed malignant tumors. Detailed comparison of comparable groups of patients with and without associated osteoarthropathy revealed many similarities and very few differences. Various theories concerning the possible cause of hypertrophic pulmonary osteoarthropathy are
presented, including a detailed description of the neurogenic theory favored by us.

**Resumen**

Los protocolos de 1,888 casos de neoplasia pulmonar operados en la clínica Mayo entre 1953 y 1963 han sido revisados. La incidencia de osteopatía hiperтроfica neumática en el total de casos, incluyendo las neoplasias pulmonares tanto benignas como malignas así como las metástasis tumorales pulmonares, fue 9.2%. La osteopatía hiperтроfica neumática se observó en todas las variedades citológicas del carcinoma broncogénomo primario, excepto en el adenoma bronquial a células cilíndricas y en tumores malignos mixtos. La comparación en detalle de grupos comparables de pacientes, con y sin osteopatía hiperтроfica asociada, reveló muchas similitudes y muy pocas diferencias. Las varias teorías relativas a la causa de la osteopatía hiperтроfica son espuestas, incluyendo la descripción detallada de la teoría neurogénica, favorecida por el autor.

**Zusammenfassung**


**Referencias**