

A Study of Paraneoplastic Syndrome Patterns in Patients with Bronchogenic Carcinoma

Vurgese Thomas Abraham, MD, MRCP (UK)* Bahl Sunil Radhakrishna, MBBS, MD**
Mapkar Osman Abdulwahab, MBBS, MD*

Background: Paraneoplastic syndromes, which are the distant effect of underlying carcinoma, which can present early, well before the primary lung lesion produces local symptoms and even when the tumor is undetected or very small. Paraneoplastic syndromes are common in patients with bronchogenic carcinoma. They may be the presenting finding or the first sign of recurrence.

Aims: To assess the incidence and pattern of paraneoplastic syndrome (PNS) in patients with bronchogenic carcinoma.

Settings: Peripheral Hospital in Kuwait.

Design: Retrospective study.

Methods: A retrospective study of 52 confirmed bronchogenic carcinoma patients occurring from January 2000 to June 2004 in our hospital was carried out. The Medical records of all the confirmed cases of bronchogenic carcinoma admitted between January 2000 and June 2004 were reviewed. The clinical and biochemical parameters recorded were: age, sex, underlying medical illness, presentation complete blood count, blood urea, electrolytes and serum calcium levels, and appropriate hormone levels where indicated. The localization of the tumors was done by chest x-ray and CT scan. Tissue biopsy was obtained by bronchoscopy or under CT scan guidance and histopathological examination of the specimen was carried out. The type and pattern of PNS if any was noted. These parameters were entered into a database and later analyzed.

Statistical analysis used: The data management and statistical package used was Epi Info version 6 provided readily by the CDC (Centre for Disease Control) Bethesda USA.

Results: Forty-nine patients were male and 3 were females. All were heavy smokers or ex-smokers. The histological types were 12 (22.4%) small cell carcinoma and 40 (67.6%) non-small carcinoma. The mean age 67.46 ± 12.15 years. Associated illness found was diabetes mellitus (DM) – 24 (46%), hypertension - 33 (63.6%), and chronic obstructive pulmonary disease (COPD) - 14 (27%). Almost all the patients presented with cough – 52 (100 %), shortness of breath (SOB) - 51 (99%), haemoptysis – 22 (42%), pleural pain – 16 (31%) and fever - 22 (42%) and weight loss – 39 (75%). The PNS found were: Hypercalcemia – 22 (42%), thrombocytosis – 5 (9.6%), limbic encephalitis – 3 (5.8%), SIADH – 3 (5.8%), peripheral neuropathy – 2 (3.8%), GBS – 1 (1.9%), pancytopenia – 3 (5.8%). There was no case with ACTH secretion or Lambert-Eaton syndrome.

* Department of Medicine

**Department of Haematology

Jahra Hospital

Kuwait

Conclusions: Hypercalcemia, thrombocytosis, SIADH, pancytopenia, limbic encephalitis and other unexplained neurological problems occurring in the middle aged or elderly smokers should arouse the suspicion of an occult bronchogenic carcinoma.

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The prevalence of smoking among Kuwaiti men is very high and a large number of them are heavy smokers¹. The number of women smokers is also steadily rising. Hence the incidence of bronchogenic carcinoma is very high. It is also the cancer with the highest incidence of paraneoplastic syndromes (PNS)². PNS is a constellation of signs and symptoms that are not attributable to direct primary effects of the tumor or its metastases (secondary effects) but occurs as a consequence of biologically active chemicals produced by the tumor or through some other hitherto unknown mechanism. As PNS may be the initial presentation even before the manifestation of the tumor, even before primary or secondary effects are apparent, a high degree of suspicion is required for early diagnosis and treatment leading to a better prognosis³. The aim of the study was to determine the pattern of PNS in patients with bronchogenic carcinoma.

METHODS

The Medical records of all confirmed cases of bronchogenic carcinoma admitted between January 2000 and June 2004 were reviewed. The clinical and biochemical parameters recorded were: age, sex, underlying medical illness, presentation complete blood count, blood urea, electrolytes and serum calcium levels. The localization of the tumors was investigated by chest x-ray and CT scan. Tissue biopsy was obtained by bronchoscopy or under CT scan guidance and histopathological examination of the specimen was performed. The type of PNS if any was noted. These parameters were entered into a database and later analyzed. The data management and statistical package used was Epi Info version 6 provided readily by the CDC (Centre for Disease Control) Bethesda USA.

RESULTS

A total of 52 patients were studied comprising 49 males and 3 females – all of them were heavy smokers or ex-smokers. Out of the 52 patients with bronchogenic carcinoma, 39 patients were found to have paraneoplastic syndrome of which 37 were males and 2 were females. The mean age was 67.46 ± 12.15 years. Associated illness found was diabetes mellitus – 24 (46%), hypertension - 33 (63.6%), and chronic obstructive pulmonary disease - 14 (27%). All the patients presented with cough, 51 (99%) shortness of breath, 22 (42%) with haemoptysis, 16 (31%) with pleural pain, - 22 (42%) with fever and 39 (75%) with weight loss.

Table 1: Incidence of clinical symptoms and associated illnesses with PNS

Variable	No.	%
No. of cases	52	
Age (mean ± SD)	67.46 ± 12.15	
Sex		
Male	49	94.2%
Female	3	5.8%
Male : Female ratio	16.3:1	
Associated illness		
DM	24	46%
Hypertension	33	63.6%
COPD	14	27.0%
Clinical symptoms		
Cough	52	100%
SOB	51	99%
Haemoptysis	22	42%
Pleural pain	16	31%
Fever	22	42%
Weight loss	39	75%

The patients who presented with signs and symptoms and laboratory evidence of PNS were: 22 (42%) with hypercalcemia, 5 (9.6%) with thrombocytosis, 3 (5.8%) with limbic encephalitis and SIADH each, 2 (3.8%) with peripheral neuropathy, 1 (1.9%) with GBS and 3 (5.8%) with pancytopenia.

Table 2: PNS pattern with incidence in this study

Variable	No.	%
Total cases	52	
Hypercalcemia	22	42%
Thrombocytosis	5	9.6%
Limbic encephalitis	3	5.8%
SIADH	3	5.8%
Peripheral neuropathy	2	3.8%
GBS	1	1.9%
Pancytopenia	3	5.8%

In our study there were no patients who presented with ectopic ACTH secretion, myasthenia gravis or Lambert – Eaton myasthenic syndrome.

The histopathological types of the bronchogenic carcinoma were: 12 (23%) small cell carcinoma and 40 (67%) non-small cell carcinoma. The breakdown of non-small cell carcinoma were as follows: adenocarcinoma 18 (34.6%); squamous cell carcinoma 16(30.76%); large cell undifferentiated 6 (11.53%).

The different histological types associated with PNS were as follows: Hypercalcemia -all 22 patients (100%) were associated with non small cell carcinoma; 16 patients with squamous cell carcinoma and 6 patients with adenocarcinoma; Thrombocytosis - out of the 5 patients with thrombocytosis 3 patients (60%) were found to be associated with squamous cell carcinoma and 2 patients (40%) with

small cell carcinoma; Limbic encephalitis - all 3 patients (100%) associated with small cell carcinoma; SIADH - out of the 3 patients with SIADH, 2 patients (67%) associated with small cell carcinoma and 1 patient (33%) with squamous cell carcinoma; peripheral neuropathy - out of the 2 patients with this symptom 1 patient (50%) associated with small cell and 1 patient (50%) squamous cell carcinoma; GBS-1 patient (100%) was associated with small cell carcinoma; Pancytopenia - out of the 3 patients with pancytopenia 2 patients (67%) associated with small cell carcinoma and 1 patient (33%) squamous cell carcinoma.

DISCUSSION

The fact that bronchogenic carcinoma is caused by carcinogens and tumor promoters inhaled through cigarette smoking is fully corroborated in this study where almost 100% patients were either heavy smokers or ex-smokers. The relative risk of developing bronchogenic carcinoma increases 13 fold by active smoking or ~1.5% by passive exposure to cigarette smoke.

Paraneoplastic syndrome, which is the distant effect of underlying carcinoma can present early, well before the primary lung lesion produces local symptoms and even when the tumor is undetected or very small. The signs and symptoms of the hormones and biochemical agents produced by the bronchogenic carcinoma can be detected early by clinical and biochemical means³. The bigger tumor, the more florid are the signs and symptoms of PNS. The diagnosis of occult tumor associated with PNS requires a high degree of suspicion, but still on some occasions the tumor may remain undetected and this will lead to delay in initiation of treatment³.

Hypercalcemia is the commonest PNS of bronchogenic carcinoma and is most commonly associated with the squamous cell carcinoma type, but can be associated with the other non-small cell bronchogenic carcinomas, i.e adenocarcinoma and large cell undifferentiated. Hypercalcemia is uncommon at presentation but becomes apparent as the tumor progresses⁴. Its pathogenesis is related to hormone production and is called humeral hypercalcemia of malignancy.

In our study hypercalcemia was present in 43% of the patients, which co-relates well with the other studies. Another hormone that is produced by bronchogenic carcinoma is ADH⁵. The syndrome of inappropriate ADH (SIADH) secretion is easily diagnosed by clinical and biochemical means. It results in hypotonic euvoletic hyponatremia with urinary hyperosmolarity. It is most commonly associated with small cell bronchogenic carcinoma and is caused by release of arginine vasopressin (AVP) hormone. The incidence of SIADH of 5.8% correlates well with the other studies. Sign and symptoms may precede the tumor by many months or years^{6,7}.

In our study limbic encephalitis presented as intractable epilepsy and the small associated tumors were detected as a result of the high index of suspicion. There is evidence that neoplastic neurological symptoms are immune mediated (anti-Yo antibodies)^{8,9}. Treatment is directed towards the primary tumor and the PNS may remit with the regression of the tumor.

Thrombocytosis is the commonest paraneoplastic hematological abnormality with some studies reporting incidence of up to 50%¹⁰. In our study the incidence of thrombocytosis was 9.1%. Two of our cases had pancytopenia with hypercellular marrow as in the cases reported by Raz et al^{12,13}. The other hematological PNS reported is erythrocytosis due to increased erythropoetin secretion by the tumor¹⁴. We had no cases with erythrocytosis in our study.

Since PNS can be the presenting feature of bronchogenic carcinoma, it is imperative to have a high index of suspicion and to investigate these patients fully with all available facilities. The use of 18-F fluorodeoxyglucose positron emission tomography ((U8)F]FDG-PET) has further helped in detecting small occult tumors.

CONCLUSION

Paraneoplastic syndromes are common in patients with bronchogenic carcinoma from Al Jahra region of Kuwait. These patients clinically presented with hypercalcemia, thrombocytosis, SIADH or limbic encephalitis. It is therefore important to consider the possibility of bronchogenic carcinoma in smokers who present with signs, symptoms and biochemical evidence of paraneoplastic syndromes and to investigate them thoroughly.

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