

Infections and paraneoplastic disorders in patients with solid malignancies of advanced clinical stage

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Abstract

The prevalence of disorders of infectious and paraneoplastic origins in 750 patients with solid malignancies of advanced clinical stage in various locations has been reviewed by the authors in the period from 2009 to 2019. Of the infections, pneumonia and acute exacerbation of COPD occurred most frequently. Based on the observations of the authors, it has been assessed that the bacterial infections in cancer patients are very frequently associated with severe symptoms and often lead to sepsis. Paraneoplastic disorders occurred in cancer patients very frequently. These are primarily the disorders of the haematological system and the haemostasis. Of the metabolic disorders, hyponatraemia was predominant and had a significant negative affect on the quality of life of the patients. Additionally, both in number and nature, several disorders were observed related to gastrointestinal diseases, renal involvement, autoimmune processes, and endocrine disorders.

Introduction

In patients with advanced clinical stage solid malignancies, the complex management, which is in line with professional guidelines and patient expectations, is often a major challenge for both the physicians and the nursing staff. The disease progression in cancer patients may occur due to the local and/or systemic spread of the primary malignancy, even though, all possible active oncological treatment options were tried. The symptoms of clinical progression occur upon the manifestation of infections primarily involving the lungs and the kidneys. Paraneoplastic disorders, which develop in direct or indirect association with malignancies, have a marked impact on the quality of life and life expectancy of patients. They can trigger multi-organ dysfunction syndrome and disorders. In the case of advanced malignancies, beyond the paraneoplastic disorders, it is not uncommon that pathological processes (such as acute gastrointestinal bleeding, acute pancreatitis) that cannot be associated with the primary malignancy also develop.

Patients and methods

The majority of the 750 patients with malignancy of advanced clinical stage (Table 1) assessed in the period of 10 years (from 2009 to 2019) was classified as elderly. The majority of patients (n=490) had primary lung cancer, predominantly non-small-cell lung carcinoma (NSCLC). A large number of patients were identified as having colorectal or breast cancer, and a smaller number of patients had malignancies of renal, ovarian, gastric and hepatobiliary origin (Table 2). Of the 750 patients, staging examinations confirmed locally advanced clinical stage in 640 cases (Table 3). In addition to the locally advanced disease (n=304), a similar number of multiple organ (lymphatic) metastases (n=336) has also been detected. The development of bacterial infections was detected in 378 patients (Table 4). Pneumonia was confirmed in 152 cases radiologically or by chest CT scan, and acute exacerbation of COPD was confirmed in 124 patients. The incidence of septic processes is notable (N=78), most certainly as an immune-related adverse effect of the previously administered cytotoxic chemotherapy or radiation therapy. The types and incidences of paraneoplastic disorders,

directly or indirectly associated with malignancies are summarised in Tables 5 and 6. Of the paraneoplastic disorders, the disorders of the haematological system and the haemostasis occurred most frequently in cancer patients. A large number of patients had metabolic (n=529), cardiac (n=417) and gastrointestinal (n=317) disorders, while kidney, immunological and endocrine disorders affected a smaller number of patients [1-13].

Table 1. General characteristics of the patients with solid carcinoma

Period reviewed	2009-2019
Number of cases	n=750
Male	n=410
Female	n=340
Age	48 to 79 years
Mean age	61 years

Table 2. Classification of tumorous processes based on localisation

Tumour location Primary lung cancer NSCLC: n=386 SCLC: n=104	Number of cases (n) 490
Colorectal	65
Breast	82
Gastric	16
Hepatobiliary	26
Kidney-urinary bladder	36
Ovarian	29
Malignant melanoma	6

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Table 3. Dissemination of the disease

Type of localisation	Number of patients (n)
Locally advanced disease	304
Multiple organ metastases	218
Lymphatic involvement	118
Severe non-cancerous disease (heart, lung, kidney, metabolic diseases)	100

Table 4. Infectious diseases

Type of infection	Number of cases
Acute pneumonia	152
Acute exacerbation of COPD	124
Acute pyelonephritis	22
Sepsis	78
Necrotising fasciitis	2

Table 5. Paraneoplastic disorders in our cancer patients

Haematological disorders	
The type of abnormalities	Number of patients
Anaemia (Hgb ≤ 100 g/L)	335
Leukopaenia (leukocyte count ≤ 1.5 × 10 ⁹)	69
Leukocytosis (leukocyte count ≥ 10.8 × 10 ⁹)	193
Thrombocytopenia (platelet count ≤ 80 × 10 ⁹ /L)	48
Autoimmune haemolytic anaemia	6
Pure red-cell aplasia	2
Haemostatic disorders	
Thrombophlebitis (superficial)	116
Acute deep vein thrombosis	108
Acute pulmonary embolism	79
Acute disseminated intravascular coagulation	4
Thrombotic thrombocytopenic purpura	2
Gastrointestinal disorders	
The type of abnormalities	Number of cases
Acute gastrointestinal bleeding	89
Acute pancreatitis	45
Hepatic dysfunction of various severities	172
Acute mesenteric ischaemia	12

Discussion

Paraneoplastic disorders and infections, frequently developing in cancer patients of advanced clinical stage, are of notable importance in terms of the quality of life of patients and adversely affect life expectancies. Timely identification of the extremely complex paraneoplastic disorders associated with different organ manifestations is of essential importance, otherwise no effective treatment can be ensured. The recognition of symptoms is impeded by the fact that often multiple paraneoplastic disorders develop simultaneously, and the identification of the less evident abnormalities related to dominant symptoms is delayed. The large number of paraneoplastic disorders demonstrates that solid malignancies include not only the disorder of the affected organ but also affect the physical and mental status of the entire body, i.e. a malignancy of any stage can be considered systemic in every case. Often, the development of paraneoplastic symptoms cannot be explained by the local invasion and/or metastasis (metastases) of the tumour: they are rather the result of the abnormal hormone, protein or cytokine production of the tumour [5,7,12]. The role of the immune response of the body can be considered and often confirmed too: primarily, tumour antigens in the different tumour tissues can induce an immune response, and as a consequence inflammation may develop even in the otherwise intact tissues [5]. In the case of paraneoplastic

syndromes the clinical symptoms are similar to those of primary endocrine, dermatological, rheumatological, haematological and neuromuscular diseases [5,12,13].

In addition to the development of paraneoplastic disorders, the occurrence of bacterial infections is also of great importance. Inflammation induced by bacterial infection has been identified in nearly 50% (n=378) of the assessed 750 cancer patients in advanced stage. The most common inflammations were the development of pneumonia (n=152) and acute exacerbation of COPD (n=124). A large number of septic complications occurred (n=78) and in these patients septic fever, marked leukocytosis, blood test - left shift, highly elevated CRP, and positive procalcitonin test were observed. In the majority of cases, chest radiography and chest CT scans confirmed very severe inflammations with pleural effusion and frequent cavitation of the infiltrative lesions. Severe pyuria, highly elevated CRP, and septic symptoms were frequently noticed in inflammatory processes involving the kidneys.

Of the paraneoplastic disorders, haematological disorders were predominant in our patients (n=551) (Table 5). Of the haematological disorders, anaemia occurred most frequently (n=335), nearly 30% of the cases were iron deficiency anaemia and nearly 10% of the cases were B12 and folic acid deficiency anaemia. Anaemia induced by bone marrow infiltration of the malignant cells was observed in 8% of our cases. The

Table 6. Paraneoplastic disorders in cancer patients

Cardiac disorders	
The type of abnormality	Number of patients (n)
Congestive heart failure (Systolic left ventricular dysfunction)	144
Ischaemic heart failure	126
Tachyarrhythmia with atrial fibrillation	98
Pericardial effusion	29
Metabolic disorders	
The type of abnormality	Number of cases (n)
Hyperglycaemia	98
Hyperglycaemia with ketoacidosis	69
Hyperuricaemia	179
Hypercalcaemia	49
Type-B lactic acidosis	12
Hyponatraemia (SIADH)	183
Hypoglycaemia	49
Renal involvement	
Disorders	Number of cases (n)
Acute pyelonephritis	49
Acute pyelonephritis with sepsis	26
Acute renal failure	53
Asymptomatic proteinuria/microhaematuria	68
Renal vein thrombosis	2
Autoimmune disorders	
Diagnoses	Number of cases (n)
Rheumatoid-like arthritis (acute polyarthritis)	52
Immune hepatitis	4
Pleuritis-pneumonitis	34
Acute pericarditis	28
Dermatomyositis	2
Endocrine disorders	
Diagnoses	Number of cases (n)
Adrenal cortex insufficiency (Addison's disease)	16
Hypothyroidism	10
Hyperthyroidism	12

frequency of quantitative leukocyte and platelet abnormalities was nearly 20%. Immune haemolytic anaemia and pure red-cell anaemia was confirmed in six and two patients, respectively.

Haemostatic disorders were also often diagnosed (Table 5). In addition to superficial (in several cases migratory) thrombophlebitis, 178 cases of acute deep vein thrombosis and acute pulmonary embolism occurred. It is noteworthy that 50% of the manifestation of the acute pulmonary embolism cases were asymptomatic ("silent"), primarily in patients with primary pulmonary malignancy [3,11].

Of the gastrointestinal and hepatobiliary disorders, 89 cases of acute gastrointestinal bleeding and 172 cases of hepatic disorder of various degrees of severity were observed. Cases of acute pancreatitis and acute mesenteric ischemia also occurred. The presence of liver metastases was the primary cause of abnormal liver functions; hepatic lesions of toxic origin, cholangitis and cholangiosepsis occurred more rarely.

A significant proportion of cardiac disorders cannot be directly attributed to malignancies. However, of the 29 patients with pericardial effusion, the development thereof was clearly related to the malignant process (pericarditis carcinomatosa) in 18 cases. Systolic left ventricular dysfunction, ischaemic heart disease, and tachyarrhythmia with atrial fibrillation were observed most frequently.

Of the metabolic disorders, 98 cases of hypercalcaemia and 69 cases hyperglycaemia with ketoacidosis were observed. Prolonged glucocorticoid therapy, infections, immunosuppressive therapy, repeated transfusions and cachexia predispose to the aforementioned conditions. In cancer patients under treatment, hyperuricaemia develops often, sometimes concomitantly with hypercalcaemia and hyperphosphataemia [8,9,13]. The acute tumour lysis syndrome occurs rarely in patients with solid malignancies, and rather develops in patients under therapy for acute haemoblastoses or malignant lymphomas. Type-B lactic acidosis occurs rarely and its exact cause is unclear but mainly the tissue hypoperfusion due to microemboli caused by circulating tumour cells, and the increased anaerobic metabolism triggered by this can lead to acidosis [13]. The development of hyponatraemia is a very common and severe metabolic disorder in solid malignancies [9]. Acute, severe hyponatraemia may cause nausea, vomiting, headache, severe muscle weakness, generalised seizures, and coma. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterised by hypo-osmotic euvolemic hyponatraemia (134 mEq/L) and increased urine osmolality (100 mOsm/kg). In cancer patients this syndrome arises from tumour cell production of antidiuretic hormone (ADH: arginine vasopressin), and atrial natriuretic peptide [13].

Kidney lesions did not occur frequently in our patients. Inflammatory processes were predominant. Acute kidney failure mainly occurred due to acute disseminated intravascular coagulation, haemolytic anaemia and thrombotic thrombocytopenic purpura. The use of antineoplastic medicinal products can be complicated by acute

renal failure, and sepsis and renal infiltration of malignant cells should be considered as predisposing factors [6,7]. Asymptomatic proteinuria and microhaematuria without abnormal kidney functions were observed in 68 patients. It is well known from clinical experience that the properly functioning immune system has a protective role against the development of malignancies. In severe immunodeficiencies ("immunocompromised" states), both solid malignancies (breast, prostate, lung, colon, ovarian) and oncogenic viral (herpesvirus type 8, and Epstein-Barr virus) infection-related diseases Kaposi's sarcoma and B-cell non-Hodgkin's lymphoma develop more frequently [5]. Autoimmune conditions are primarily caused by autoantibody production against tumour cells (tumour antigens). These autoantibodies can induce immunological disorders in different organs (joints, lungs, serous membranes, skeletal muscles, kidneys) [1,2,5]. In our cases, symptoms of polyarthritis were predominant, (n=52) (Table 6). Severe dermatomyositis was observed in two patients with renal tumour. Cases of serositis were observed in 62 patients.

Of endocrine disorders, adrenal insufficiency, hypothyroidism and hyperthyroidism occurred in 16, 10 and 12 patients, respectively. Of the neurological disorders, peripheral neuropathy was observed in 8 patients with small-cell lung cancer. (Lambert-Eaton syndrome) [12].

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