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

Géza Bozóky* and Éva Ruby
Department of Pulmonology, Hospital of Bács-Kiskun County Municipality, Kecskemé, Hungary

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

*Correspondence to: Géza Bozóky, Department of Pulmonology, Hospital of Bács-Kiskun County Municipality, Kecskemé, Hungary, E-mail: bozokygy@freemail.hu

Key words: advanced-stage malignancy, severe infection, paraneoplastic disorders, multi-organ dysfunction syndrome

Received: August 01, 2020; Accepted: August 14, 2020; Published: August 19, 2020
Infections and paraneoplastic disorders in patients with solid malignancies of advanced clinical stage

Infections and paraneoplastic disorders are of notable importance even in the otherwise intact tissues [5]. In the case of paraneoplastic disorders, tumour antigens in the different tumour tissues can induce a response of the body that can be considered and often confirmed too: cytokine production of the tumour [5,7,12].

The role of the immune system 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, 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 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.

The type of abnormality Number of patients (n)

| Type of abnomality | Number of patients |
|--------------------|--------------------|
| Anaemia (Hgb<100 g/L) | 335 |
| Leukopaenia (leukocyte count≤1.5×10⁹) | 69 |
| Leukocytosis (leukocyte count≥10.8×10⁹) | 193 |
| Thrombocytopenia (platelet count≤50×10⁹/L) | 48 |
| Autoimmune haemolytic anaemia | 6 |
| Pure red-cell aplasia | 2 |

Cardiac disorders

The type of abnormality Number of patients (n)

| Type of abnormality | Number of patients |
|--------------------|--------------------|
| Congestive heart failure | 144 |
| Ischaemic heart failure | 126 |
| Tachyarrhythmia with atrial fibrillation | 98 |
| Pericardial effusion | 29 |

Metabolic disorders

The type of abnormality Number of cases (n)

| Type of abnormality | Number of cases |
|--------------------|----------------|
| Hyperglycaemia | 98 |
| Hyperglycaemia with ketoacidosis | 69 |
| Hyperuricaemia | 179 |
| Hypercalcaemia | 49 |
| Type-B lactic acidosis | 12 |
| Hypopatremia (SIADDH) | 183 |
| Hypoglycaemia | 49 |

Renal involvement

The type of abnormality Number of cases (n)

| Type of abnormality | Number of cases |
|--------------------|----------------|
| 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)

| Diagnoses | Number of cases |
|-----------|----------------|
| Rheumatoid-like arthritis (acute polyarthritis) | 52 |
| Immune hepatitis | 4 |
| Pleuritis-pneumonitis | 34 |
| Acute pericarditis | 28 |
| Dermatomyositis | 2 |

Endocrine disorders

Diagnoses Number of cases (n)

| Diagnoses | Number of cases |
|-----------|----------------|
| Adrenal cortex insufficiency (Addison's disease) | 16 |
| Hypothyroidism | 10 |
| Hyperthyroidism | 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 expectations. 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].
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 euvoletic hyponatraemia (134 m Egr/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].

References

1. Azar I, Khasnis A (2013) Paraneoplastic rheumatologic syndromes. Curr Opin Rheumatol 25: 44-49.
2. Bojinka V, Janta I (2012) Rheumatic diseases and malignancies. Medica I Clin Med 7: 364-371.
3. Bozóky G, Ruby É (2018) Acute silent non-massive (submassive) pulmonary embolism. Am I Ang and Surg 1: 001-003.
4. Carella A, Marinelli T, Pumppo M, Benvenuto E (2015) Metabolic disorders in hematologic malignancies-A review. Archives of Medicine 7: 1-8.
5. Prakash O, Gill J, Farr G (2002) Immune disorders and susceptibility to neoplasms. Ochsner J 4: 107-111. [Crossref]
6. Humphreys BD, Soiffer RJ, Magee CC (2005) Renal failure associated with cancer and its treatment: an update. J Am Soc of Nephrol 16: 151-161. [Crossref]
7. Darmon M, Ciroldi M, Thiery G, Schlemmer B, Azoulay E (2006) Clinical review: Specific aspects of acute renal failure in cancer patients. Crit Care 10: 211. [Crossref]
8. Maesaka JK, Imbriano L, Mattana J, Gallagher D, Bade N, et al. (2014) Differentiating SIADH from cerebral renal salt wasting: failure of the volume approach and need for a new approach to hyponatraemia. J Clin Med 3: 373-385. [Crossref]
9. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, et al. (2013) Diagnosis, evaluation, and treatment of hyponatraemia: expert panel recommendations. Am J Med 126: 91-47. [Crossref]
10. Bozóky G (2019) Community-acquired pneumonia as a cause of sepsis. Trends Med 19: 1-4.
11. Bozóky G (2007) Disorders of the haemostatic system in patients with solid malignancies. In: Handbook of hematology. Editors: Tondre C, Lebéque C, pp: 317-318.
12. Bataller Dalman J (2003) Paraneoplastic neurologic syndromes: approaches to diagnosis and treatment. Semin Neurol 23: 215-224.
13. Androge HJ, Madias NE (2000) Hyponatraemia. N Engl J Med 342: 1581-1589.

Copyright: ©2020 Bozóky G. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.