Current practice


Paraneoplastic granulocytosis in an advanced lung cancer patient

Polynucléose paranéoplasique chez un patient présentant un cancer du poumon

Audrey Le Roy1
Pierre Pasquier1
Dillon Savard2
Sarah Bugier3
Stéphane Merat1
Jean-Etienne Pilo3
Hervé Delacour3
1 Bégin Military Teaching Hospital, Intensive Care Unit, Saint Mandé, France
2 Family Medicine Residency, David Grant Medical Center, California, USA
3 Bégin Military Teaching Hospital, Department of biology, Saint Mandé, France
<herve.delacour@santarm.fr>

Abstract. Paraneoplastic syndromes (PNPs) refer to cancer-associated signs and symptoms arising in organs and tissues that are remote from the cancer and unrelated to metastasis. Currently the best described PNPs are attributed to tumor secretion of functional peptides and hormones or immune cross-reactivity between tumor and normal host tissues. Paraneoplastic hematologic syndromes are observed more rarely. Here we report a case of paraneoplastic granulocytosis in an advanced lung cancer patient.

Key words: paraneoplastic syndromes, lung neoplasms

Résumé. Les syndromes paranéoplasiques correspondent à un ensemble de symptômes cliniques et/ou d’anomalies biologiques associés à certains cancers mais non liés à l’envahissement tumoral local ou métastatique. Les syndromes paranéoplasiques endocriniens (sécrétion ectopique d’une hormone ou d’une pseudo-hormone) et neurologiques (liés à une réaction immunitaire croisée par similitude antigénique entre la tumeur et le système nerveux central ou périphérique) sont les plus connus. Les syndromes paranéoplasiques hématologiques sont plus rarement observés. Nous rapportons un cas de polynucléose paranéoplasique chez un patient présentant un cancer du poumon.

Mots clés : syndrome paranéoplasique, cancer du poumon

Paraneoplastic syndromes (PNPs) refer to cancer-associated signs and symptoms arising in organs and tissues that are remote from the cancer and unrelated to metastasis [1]. It is estimated that PNPs affect up to 8% of patients with cancer [2]. Currently the best described PNPs are attributed to tumor secretion of functional peptides and hormones (e.g. the syndrome of inappropriate antidiuretic hormone (SIADH)) or immune cross-reactivity between tumor and normal host tissues (e.g. Lambert-Eaton myasthenic syndrome (LEMS)) [1]. Paraneoplastic hematologic syndromes are observed more rarely. Here we report a case of paraneoplastic granulocytosis in an advanced lung cancer patient.

Case presentation

A 63 year-old man was admitted in our ICU for a coma secondary to generalized tonic-clonic seizures. The patient had an 80 pack-year smoking history, having smoked for 30 years. Two months before his admission, the patient had contacted his primary care physician because of persistent right rib pain secondary to a fall. A chest X-ray revealed a well circumscribed soft tissue mass in right upper chest, suspected of being a lung cancer. Clinical examination on admission was unremarkable, with no hepatosplenomegaly or adenopathy observed, in particular. Laboratory investigation revealed an extreme leukocytosis of 138 G/L, associated with an inflammatory syndrome as evidenced by elevated C-reactive protein (267 mg/L) and fibrinogen (5.98 g/L) and an inconclusive elevation of procalcitonin (1.4 ng/mL; normal range: < 0.4 ng/mL). One year prior to this measurement, the patient’s leukocyte count was normal. Peripheral blood smear examination confirmed the leukocytosis with a normal differentiation and complete maturation (neutrophils: 97 %, lymphocytes: 2%, monocytes: 1%) (figure 1). LDH was elevated at 901 U/L (normal range: 249 – 413 U/L). The results of the remaining laboratory tests were in the normal range including blood urea and creatinine levels, and transaminases. A cranial CT-scan revealed multiple areas of tissue damage surrounded by oedema, which was suggestive of cerebral
Current practice

Figure 1. Peripheral blood smear. Extreme leucocytosis with normal differentiation and complete maturation (neutrophils 97%, lymphocytes 2%, monocytes 1%) (Giemsa stained peripheral blood smear x 100 – picture A – and x 1,000 – picture B).

Figure 2. Cerebral CT scan. Multiple necrotic metastases in right frontal, left parietal and temporal lobes, surrounded by oedema. In the middle picture, beginning of supratentorial engagement.

metastasis of his suspected lung cancer (figure 2). Resuscitative measures were introduced (sedation, intracranial pressure monitoring, vasopressive drugs and mechanical ventilation). Empiric antibiotic treatment was given as well (amoxicillin/clavulanate, 6 g per day for 7 days) to treat a probable aspiration pneumonia, which may have happened during the initial coma. Cultures of the patient’s CSF, blood, urine and broncho-alveolar lavage fluid were negative, as were *L. pneumophila* and *S. pneumoniae* urinary antigens. A CT scan with IV contrast of his chest, abdomen and pelvis revealed a 12 cm lung tumor in the right upper lobe associated with osteolysis of the patient’s right ribs (figure 3). Multiple bilateral pulmonary nodules (including one 22 mm nodule in the lingula) were observed with enlarged lymph nodes in the mediastinum and in the right hilar and cardiophrenic regions. Pulmonary edema in the upper lobes was consistent with acute respiratory distress syndrome. Two necrotic metastases were seen in the adrenal glands (58 mm on the right and 45 mm on the left) and one in the pancreas. Peritoneal carcinosis was seen as well. A CT-guided biopsy of the right upper-lobe tumor confirmed the diagnosis of non-small cell lung carcinoma. Immunohistochemical study showed an expression of TTF1 and CKAE4/5 and histological findings revealed a poorly differentiated tumor, with various areas of necrosis. On day 7, a significant decrease in the patient’s C-reactive protein (40 mg/L) was observed while the white blood cell count remained essentially unchanged (leucocytes: 121 G/L). Unfortunately the patient died on Day 8 with multiple organ failure.

Discussion

An increased level of white blood cells (WBC) is often observed in cancer patients either at the time of diagnosis or during the course of the disease. In such patients, several factors may contribute to leukocytosis: hematopoietic growth factors used during the treatment course, infection, paraneoplastic granulocytosis, glucocorticoids or vasopressor administration, and newly diagnosed leukemia.
Paraneoplastic granulocytosis (PNG) has been encountered in a variety of solid tumors including small cell and non-small cell lung cancer, hepatocellular carcinoma, pancreatic adenocarcinoma, sarcoma, bladder carcinoma, glioblastoma, nasopharyngeal carcinoma, esophageal small cell carcinoma, and melanoma [3]. PNG is caused by the paraneoplastic production of hematopoietic growth factors. Asano et al. published the first report of colony stimulating factor (CSF) producing lung cancers, characterized by the development of extreme neutrophilia. The neutrophilia was transferred to nude mice by the transplantation of tumor cells [4]. Several subsequent investigations demonstrated elevated serum concentrations of GCSF, GMCSF and IL-6 in patients with lung cancer and extreme neutrophilia [5-7].

The incidence and characterization of PNG in patients with lung cancer was well described by Kasuga et al. [5]. In a seven year study, they investigated 227 lung cancer patients. Among them, 33 were diagnosed with PNG (14.5%). Leukocyte counts typically ranged from 10 to 40 G/L but in 6 patients (2.6%) the leukocyte count exceeded 50 G/L and in one patient leukocytes were 100 G/L. Such extreme leukocytosis (also called leukemoid forms or leukemoid reactions) are occasionally reported in the literature [5, 7, 8]. In the investigation published by Kasuga et al., only one patient with PNG exhibited small cell lung carcinoma. All the other patients had non-small cell lung carcinoma, with the highest incidence being that of large cell carcinoma. Patients with large cell carcinoma also had the highest incidence of leukemoid forms. It is unclear whether or not the tumor size is related to the level of leukocytosis. However Kaminska et al. reported a positive relation between IL-6 levels and the tumor size of patients with non-small cell lung carcinoma.

The diagnosis of PNG implies the exclusion of other etiologies of leukocytosis previously mentioned. The diagnostic approach is based on drug history, on clinical examination in order to identify any sign of infection and on laboratory investigations. In this case, iatrogenic leucocytosis as well as infection were easily ruled out, since there was no history of treatment with hematopoietic growth factors nor of glucocorticoids or vasopressor administration, the patient was never febrile, and all cultures remained sterile. Moreover, empiric antibiotic treatment failed to affect the leukocyte levels, though the CRP level did drop significantly. In this case, the main challenge in narrowing the differential diagnosis arose between PNG and hematological neoplasia, in particular chronic myelogenous leukemia (CML). We were unable to test for the BCRABL fusion gene and the JAK2 V617F gene mutation to formally rule out a hematological neoplasia. However, several factors allowed us to exclude these etiologies. First, the patient had no splenomegaly or hepatomegaly. Also the patient’s leukocyte differentiation was predominantly neutrophils and was not accompanied by blastosis, myelemia, basophilia or eosinophilia. This rendered hematological neoplasia unlikely, leaving the diagnosis of PNG. Blood-cytokine levels (GCSF, GMCSF or IL-6), which could confirm this diagnosis, were not performed due to the rapidly fatal evolution of the disease.

Once other etiologies are ruled out, paraneoplastic granulocytosis does not require specific therapy. In contrast to leukemic blasts, which may cause hyperviscosity and vaso-occlusion at counts as low as 20 G/L, the mature, deformable neutrophils that characterize paraneoplastic granulocytosis are unlikely to cause leukostosis below a count of 250 G/L, and therefore do not require leukopheresis. Successful treatment of the underlying tumor often
improves this condition [9, 10]. While PNG does not require specific therapy, it is generally associated with a poor prognosis in patients with lung carcinoma. Today, it is unclear whether these tumors respond differently to standard or experimental therapy, and whether the paraneoplastic process is indicative of an aggressive tumor phenotype. Kasuga et al. reported that, when controlling for important prognostic factors (disease stage and patient age), patients with PNG had a poor outcome compared with patients without leukocytosis (median survival: 4.6 months in the PNG group vs. 20.8 months in the non-PNG group, \( p < 0.001 \)) [5].

**Conclusion**

Paraneoplastic granulocytosis with extreme leukocytosis is an uncommon paraneoplastic syndrome in lung cancer. Its diagnosis requires the exclusion of other etiologies of leukocytosis, mainly infections and hematological neoplasia. In this case, even though molecular biology investigations were not realized to formally exclude a hematological malignancy, we provide indirect arguments to assess the diagnosis of paraneoplastic hyperleukocytosis associated with primary lung carcinoma. Patients with paraneoplastic granulocytosis tend to have a poorer outcome compared to others, partially due to bad response to chemotherapy and radiotherapy, and our patient unfortunately illustrated this tendency.

**Conflicts of interest:** none.

**References**