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Pneumocystis in metastatic lung cancer, a pragmatic approach in support of prophylaxis

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SUMMARY

Lung cancer prognosis has improved in the last decade, including in patients with brain metastasis. However, few of these patients who receive corticosteroids have a primary prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP). We report the case of an 80-year-old man diagnosed with non-small cell lung cancer and concomitant symptomatic brain metastases, treated with 50 mg/day of prednisolone without any prophylaxis, who presented an acute PJP. After 72 hours of unsuccessful treatment of PJP, the patient died. In our review of this case and the existing literature, we emphasise the importance of a wide use of prophylaxis for PJP, especially in advanced lung cancer treated with corticosteroid therapy. We discuss this issue and report current evidence for primary prophylaxis by trimethoprim–sulfamethoxazole.

BACKGROUND

Human pneumocystosis is a fungal infection caused by *Pneumocystis jirovecii*, a cosmopolitan and opportunistic ubiquitous fungus. *P. jirovecii* pneumonia (PJP) is potentially lethal, developing mainly in the lungs of profoundly immunocompromised patients. HIV infection, organ transplants and haematological malignancies are well-defined risk factors.[1 2]

A review of the literature provided arguments to consider a pathophysiological association between *P. jirovecii* and the use of corticosteroids, and American Thoracic Society (ATS) guidelines recommend prophylaxis when prednisone doses exceed 20 mg/day for longer than 1 month.[3]

We present a case of a lethal PJP in a patient with metastatic lung cancer who received corticosteroids without prophylaxis.

CASE PRESENTATION

In August 2015, an 83-year-old HIV-negative, non-smoker Caucasian man was diagnosed with T3N2M0 small cell lung carcinoma. He went into complete remission after six cycles of carboplatin/etoposide and thoracic radiation (30 Gy with daily fractions of 3 Gy).

In December 2016, a stage I (pT1N0M0) right lower lobe lung adenocarcinoma was discovered and treated with lobectomy. The tumour had no EGFR, BRAF or KRAS mutation and no ALK, ROS1, RET rearrangement; only a copy number variation of MET gene (two to three copies). In April 2017, a neurological impairment revealed a frontal brain metastasis. The patient was treated with radiotherapy associated with methylprednisolone initially at 100 mg/day and then reduced to 50 mg/day.

In June 2017, he presented dry cough and shortness of breath associated with self-reported fever. Two days after the first symptoms, he was admitted to hospital. At admission, he had fever (38.2°C), blood pressure was 108/61 mm Hg, regular pulse of 79 bpm, respiration of 18 cycles/min, and 95% SpO_2 with 2 L/min of oxygen supplementation. There was no recent chemotherapy, and no immunosuppressive treatment other than corticosteroids.

INVESTIGATIONS

Blood laboratory tests revealed no cytopenia: haemoglobin concentration 129 g/L, platelet count 244 000×10^9/L, white cell count 6400/mm^3, including neutrophil count 3900/mm^3. There was no renal dysfunction with an estimated glomerular filtration rate of >60 mL/min. Chest CT scan showed bilateral excavated nodules evoking lung abscesses, associated with diffuse bilateral ground-glass opacities (figure 1). A bronchoalveolar lavage (BAL) was immediately performed with good tolerance, for bacteriological and mycological analyses. Blood culture and serum galactomannan antigen were negative.

DIFFERENTIAL DIAGNOSIS

A posteriori, BAL results revealed the presence of *P. jiroveci* (with Gomori-Grocott staining, indirect immunofluorescence and positive *Pneumocystis* PCR at the 21st cycle of amplification), as well as a few colonies of *Aspergillus fumigatus* in culture, *Actinomyces odontolyticus* (10^5 UFC/mL) in culture and *Nocardia nova* susceptible to trimethoprim–sulfamethoxazole (TMP–SMX).[4]

To explain the acute respiratory failure, we discarded the role of *A. odontolyticus*, which is probably a contamination during the BAL procedure. Images of lung abscesses are compatible with *N. nova*, but nocardiosis would not explain the rapid clinical degradation. *A. fumigatus* could be implicated in respiratory failure, but the patient had no neutropenia and a negative *A. fumigatus* PCR in BAL, making the possibility of rapidly lethal invasive aspergillosis less likely.

The association of diffuse bilateral ground-glass opacities, very low cycle threshold value of *Pneumocystis* PCR in BAL, a positive direct examination and a deep hypoxaemia progressing into severe acute respiratory failure are solid arguments to attribute the death of the patient to a PJP, rather than other coinfections.

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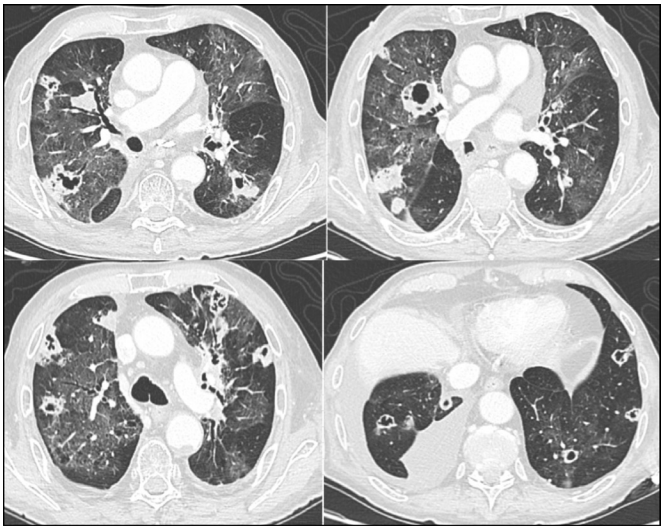

Figure 1 Chest CT scan with bilateral excavated nodules evoking lung abscesses, associated with diffuse bilateral ground-glass opacities.

TREATMENT

First, the patient was treated with ceftriaxone and rovamycin as recommended for community-acquired pneumonia with comorbidities and severity criteria. After the chest CT, intravenous voriconazole and TMP–SMX treatment was started. Corticosteroids were maintained as adjuvant therapy of hypoxaemic PJP.

OUTCOME AND FOLLOW-UP

His clinical situation worsened on a respiratory level with increasing oxygen needs. Despite 48 hours of probabilistic treatment, his respiratory failure became critical. On arterial blood gas, he presented an extremely severe hypoxaemia despite oxygen supply (flow rate 15 L/min) with a PaO_2 measured at 39 mm Hg. The patient died on day 3.

DISCUSSION

In patients with lung cancer, especially with brain metastasis, corticosteroids are commonly prescribed. Life expectancy is limited to a few months or years in most cases, and physicians do not prescribe chemoprophylaxis against *Pneumocystis* spp. A retrospective study showed that fewer patients with solid tumours (3.9%) received prophylaxis compared with patients with haematological malignancies (63.6%).[5]

Lung cancer is at low risk of PJP (<25 cases/100 000 patient-year) like other solid tumours, excluding central nervous system cancer.[6] But for patients having solid cancer and being treated by corticosteroids, the incidence of PJP rises to 1.3%.[7] Furthermore, PJP is usually more abrupt and fulminant[8] among patients with neoplastic disease, and its mortality rate is much higher, approaching 50%,[7 9] and a significant risk factor of mortality with an OR=2.66. In different studies, 55%–87% of patients with PJP had previously used corticosteroids, and 18%–31% had a solid tumour.[9 10] The most important predisposing factor for developing PJP is the use of steroids, even at a low dose (equivalent to ≥20 mg/day prednisone for ≥1 month).[11 12] ATS guidelines recommend prophylaxis when prednisone doses exceed 20 mg/day for longer than 1 month.

Recent guidelines[13] and two general reviews[14 15] recommend prophylaxis for patients with solid cancer receiving prolonged, high-dose corticosteroid treatment (16–25 mg of prednisolone/day or ≥4 mg dexamethasone daily for ≥4 weeks) regardless of the stage of malignancy.

Concerning the toxicity of TMP–SMX, 85% of the patients do not experience any toxic effects.[16] So, when steroids are prescribed for a patient with cancer, especially in metastatic diseases, we prioritise a pragmatic attitude: start a prophylaxis if survival exceeds 3 months.

Learning points

- Corticosteroids are a major risk factor of *Pneumocystis jirovecii* pneumonia (PJP), adding to the risk of PJP in lung cancer.
- Guidelines recommend PJP prophylaxis by trimethoprim–sulfamethoxazole (TMP–SMX) when dose >20 mg/day.
- Side effects occur in 15% of cases, and discontinuation of the prophylaxis is required in 3% of patients treated.
- Our pragmatic proposal: start a primary prophylaxis if survival exceeds 3 months, and eventually discuss alternatives in case of TMP–SMX intolerance.

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