Pneumonitis and concomitant bacterial pneumonia in patients receiving pembrolizumab treatment

Three case reports and literature review

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Abstract

Rationale: Pembrolizumab, a monoclonal antibody against the programmed cell death 1 (PD-1) protein, can induce a stable regression of some malignancies refractory to conventional chemotherapy. Despite such therapeutic benefits, pembrolizumab can induce immune-related adverse events, with pneumonitis being the most critical problem.

Patient concerns: All 3 patients complained of fever, cough, and dyspnea after a variable time interval (1–21 days) from pembrolizumab treatment.

Diagnoses: Chest computed tomography invariably showed ground glass opacity. All tests for possible infectious agents were negative. Based on high procalcitonin level, one of 3 patients was diagnosed to have accompanying bacterial pneumonia.

Interventions: All patients received antibiotics and steroid treatments (methylprednisolone, 1 mg/kg).

Outcomes: The 3 patients showed different clinical courses ranging from mild pneumonitis to rapidly progressing respiratory failure. Among the 3 patients, 2 fully recovered with steroid treatment; 1 died from superimposed bacterial pneumonia.

Lessons: The prognosis of pembrolizumab-induced pneumonitis with a superimposed bacterial pneumonia would be poor. It is important to distinguish pure pneumonitis from that with a superimposed bacterial pneumonia.

Abbreviations: BT = body temperature, CRP = C-reactive protein, CT = computed tomography, GGO = ground glass opacity, irAEs = immune-related adverse events, mAbs = monoclonal antibody, PCP = Pneumocystis jiroveci pneumonia, PCR = polymerase chain reaction, PCT = procalcitonin, PD-1 = programmed cell death 1, PD-L1 = programmed death ligand 1.

Keywords: immune-related adverse event, programmed cell death 1 inhibitor, pembrolizumab, pneumonitis, procalcitonin

1. Introduction

The monoclonal antibodies (mAbs) against programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) are immune checkpoint inhibitors blocking inhibitory T-cell activi-

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2.1. Case 1

A 52-year-old woman with metastatic colon cancer presented with high fever (38.8°C) and dyspnea (Table 1). She had been treated 1 day prior to presentation with 100mg pembrolizumab. She complained of cough productive of thick, purulent sputum. Coarse breathing sounds with crackles and wheezing were noted on auscultation of the bilateral lung fields. Oxygen saturation was 90% on room air. On the 2nd day, C-reactive protein (CRP) and procalcitonin (PCT) increased from 70mg/dL and 0.11ng/mL to 83mg/dL and 0.38ng/mL, respectively. Chest X-ray imaging and computed tomography (CT) showed ground-glass opacities (GGOs) and focal nodular consolidations on right middle lobe (Fig. 1). Based on the high PCT level, although bacterial pathogen was not identified, this case was clinically diagnosed to have accompanying bacterial pneumonia. Despite steroid (methylprednisolone, 1.0mg/kg per day) and antibiotic (piperacillin/tazobactam, 4.5g every 8 hours) treatments, the patient died from rapidly progressing respiratory failure on the 4th day.

2.2. Case 2

A 55-year-old man with metastatic nasopharyngeal cancer who was treated with 100mg pembrolizumab presented a week later complaining of fever (peak body temperature 37.8°C), dry cough, and dyspnea (Table 1). On auscultation, decreased breath sounds were noted in the left lung field without crackles. Despite a 5-day antibiotic therapy (piperacillin/tazobactam, 4.5g every 8 hours), his fever did not subside. CRP increased from 56 to 94mg/dL and initial PCT level was 0.10ng/mL. Chest X-ray imaging and CT showed GGOs on both lung fields (Fig. 1). Intravenous methylprednisolone at a dose of 1mg/kg per day was started. After methylprednisolone treatment, his fever subsided, and his symptoms immediately improved. The patient was treated with methylprednisolone for a total of 7 days.

| Case | Time interval, d | Peak BT | Dyspnea/ sputum | Crackles/ wheezing | WBC, mm³/mL | CRP, mg/dL | Sputum culture | PCP PCR | Respiratory virus test | Chest CT | Methyl-prednisolone, mg/kg | Outcome |
|------|------------------|---------|-----------------|--------------------|-------------|-------------|----------------|---------|-----------------------|----------|--------------------------|---------|
| 1    | 1                | 38.8°C  | +/+             | +/-                | 10,420      | 0.38        | No growth     | Negative| Negative              | GGO, Patchy consolidation | 1           | Death                    |
| 2    | 7                | 37.8°C  | +/-             | -/-                | 6840        | 0.10        | No growth     | Negative| Negative              | GGOs     | 1           | Survived                |
| 3    | 21               | 37.9°C  | +/-             | -/-                | 6960        | NA          | No growth     | Negative| Negative              | GGOs     | 1           | Survived                |

2BT = body temperature, CRP = C-reactive protein, CT = computed tomography, GGO = ground glass opacity, NA = not available, PCP = Pneumocystis jiroveci pneumonia, PCR = polymerase chain reaction, PCT = procalcitonin, WBC = white blood cell.

† Days from the 1st cycle of pembrolizumab treatment to pneumonitis development.

![Figure 1](image-url) Chest X-ray and computed tomography (CT) findings: ground glass opacities (GGOs) were observed on both lower lung fields and focal nodular consolidations were found on right middle lung fields (case 1); bilateral multifocal GGOs were observed (case 2); bilateral multifocal GGOs were noted with left-sided pleural effusion (case 3).

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2.3. Case 3

A 55-year-old woman with breast cancer and malignant pleural effusion who was treated with pembrolizumab (100mg) 21 days prior presented with a dry cough, dyspnea, and fever (peak body temperature 37.9°C) (Table 1). On auscultation, breath sounds were decreased without crackles. She was treated with piperacillin/tazobactam (4.5g every 8 hours) for suspected nosocomial bacterial pneumonia. Despite 10 days of antibiotic treatment, her symptoms persisted and chest CT showed GGOs on both lung fields (Fig. 1). Transbronchial lung biopsy was performed, and methylprednisolone was administered at a dose of 1.0mg/kg per day. Lung biopsy showed focal septal lymphocytic infiltration (Fig. 2). After a 10-day methylprednisolone treatment, her dyspnea resolved, her chest X-ray findings improved, and her CRP levels decreased from 52 to 4mg/dL. The patient subsequently recovered without any complications.

3. Discussion

Pneumonitis is one of the major irAEs of anti-PD-1/PD-L1 mAbs.[2] Although anti-PD-1/PD-L1 mAbs are generally recognized as safe, 27 of 578 cases (5.0%) treated with these mAbs were complicated by pneumonitis in one multicenter study.[8] The same study reported that 12% (5 cases) of these pneumonitis cases died despite steroid therapy. The mortality rate was dependent on the grade of pneumonitis: grade 1 (0%, 0 of 17), grade 2 (0%, 0 of 14), and grades 3 to 5 (42%, 5 of 12).[8] Among the 5 fatal cases, 3 died from accompanying infections. Histologic findings were diverse: interstitial pneumonitis (4 of 11), organizing pneumonia (3 of 11), diffuse alveolar damage (1 of 11), and no identified abnormalities (3 of 11).[8]

Table 2 summarizes previously published case reports on pembrolizumab-induced pneumonitis. As shown in Table 2, pembrolizumab-induced pneumonitis developed with variable intervals after treatment, ranging from 1 week to 2 years.[9–18] Pneumonitis occurred after diverse dose (median, 4 doses) of PD1 inhibitor treatment, ranging from 1 to 38 doses.[8] Regarding the risk factors for pembrolizumab-induced pneumonitis, little is known, but smoking, prior treatment, lung cancer, prior thoracic radiotherapy, and prior lung disease were suggested to promote pneumonitis development.[8,19,20] In this study, case 1 developed...
pneumonitis just 1 day after exposure to pembrolizumab. The preexisting risk factors (diffuse lymphangitic lung metastasis) might contribute to the rapid development of pembrolizumab-induced pneumonitis.

As for the radiographic findings of PD1 inhibitor-induced pneumonitis, GGOs (100%), reticular opacities (90%), and consolidation (60%) were commonly observed in the previous reports.[20] Consistently, GGOs were noted in all 3 cases, while focal consolidation was also observed in case 1.

The overall mortality rate (20.8%) in reports in Table 2 is higher than that (12%) reported in the multicenter study by Naidoo et al.[8] This difference might be due to the prompt recognition and early treatment by more experienced clinicians in the multicenter study. In the previous case reports, almost all cases were treated with steroid and more than 60% received antibiotics (Table 2).[8–18] However, descriptions of the accompanying infections were lacking (Table 2). According to the multicenter study, 60% (3 of 5) of the fatal cases had accompanying infections.[18] Similarly, in this study, the 1st case that was fatal had a superimposed bacterial pneumonia which, in combination with the pneumonitis, most likely led to the demise of the patient. Thus, it is likely that her prognosis was poor because of her superimposed infection. However, it may be difficult to distinguish pure pneumonitis from that with superimposed bacterial pneumonia. In this regard, markers like PCT could be useful to differentiate pure pneumonitis from that complicated with bacterial pneumonia. Similarly, PCT has been shown to be useful in distinguishing lung infection from interstitial lung disease and pulmonary edema.[21,22]

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