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Case report

Mesalazine-induced lung injury with severe respiratory failure successfully treated with steroids and non-invasive positive pressure ventilation

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A B S T R A C T

Drug-induced lung injury (DLI) has become more common because of the increasing number of therapeutic agents in use. Mesalazine, also known as 5-aminosalicylic acid (5-ASA), is one of the key drugs for the treatment of ulcerative colitis (UC). Although mesalazine-induced lung injury has been previously reported, few cases have included severe respiratory failure. In this report, we present a case of mesalazine-induced lung injury with severe respiratory failure, which was improved by discontinuation of mesalazine and introduction of corticosteroid therapy and ventilation support with non-invasive positive pressure ventilation (NPPV). We also review the previous literature on mesalazine-induced lung injury.

1. Introduction

Mesalazine, also known as 5-aminosalicylic acid (5-ASA), is the first-line treatment for patients with mild-to-moderate ulcerative colitis (UC), and it has been reported to be a causative agent for drug-induced lung injury (DLI) [1–24] (Table 1). Although several cases of mesalazine-induced lung injury have been reported, only one case has so far been reported of severe respiratory failure in which mechanical ventilation was used [20]. In this report, we describe a case of severe respiratory failure due to mesalazine-induced lung injury, which was improved by discontinuation of mesalazine and introduction of corticosteroid therapy and ventilation support with non-invasive positive pressure ventilation (NPPV). We also reviewed the previous literature on patients with UC who have experienced mesalazine-induced lung injury.

2. Case report

A 58-year-old woman with UC who was on mesalazine (2400 mg per day) for 2 months was transferred to our hospital because of unresolved

pneumonia. On the day of admission, she presented with wet cough, fever, and dyspnea on exertion for a week. She was a never-smoker and had no other medical illnesses. She had no allergic history to any medications.

Initial vital signs revealed a temperature of 38.3 °C, respiratory rate of 24 breaths per minute, and O₂ saturation of 91% on 4L/min oxygen via nasal cannula. Fine crackles were audible in the bilateral lung fields. There were no signs of clubbing, skin rash, or peripheral edema. Laboratory evaluation revealed white blood cell (WBC) count of 22,000/mm³ with 88% neutrophils, 8% lymphocytes, and 3% eosinophils, hemoglobin of 9.4 g/dl, and platelet count of 1,150,000/mm³. The serum levels of c-reactive protein (CRP), Krebs von den Lungen-6 (KL-6), and surfactant protein-D (SP-D) were 15.26 mg/dl, 224 U/ml (≤500), and 130 ng/ml (≤110), respectively. Both procalcitonin (0.201 ng/ml) and β-D-glucan (<2.9 pg/ml) were negative. Test results for antinuclear antibodies, rheumatoid factor, and antineutrophil cytoplasmic antibody were negative. Arterial blood gas analysis showed partial pressure of carbon dioxide (PaCO₂) of 30.1 mmHg and partial pressure of oxygen (PaO₂) of 70.8 mmHg with 4L/min oxygen via nasal cannula. A high-

Abbreviations: NPPV, non-invasive positive pressure ventilation; DLI, drug-induced lung injury; 5-ASA, 5-aminosalicylic acid; UC, ulcerative colitis; WBC, white blood cell; CRP, c-reactive protein; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D; PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen; CT, computed tomography; BAL, bronchoalveolar lavage; BALF, bronchoalveolar lavage fluid; TBLB, transbronchial lung biopsy; ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure.

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resolution CT of the chest showed bilateral and asymmetric air space consolidation and ground-glass opacity with a peribronchial and subpleural distribution (Fig. 1).

To exclude infectious etiology, we performed further bronchoscopic evaluation with bronchoalveolar lavage (BAL). Transbronchial lung biopsy (TBLB) was also performed to evaluate the histological pattern of radiological changes in the patient's lungs. Analysis of BAL fluid (BALF)

showed a total cell count of 6.56×10^5 /ml and WBC profile of 44% lymphocytes, 32.4% eosinophils, and 16% neutrophils. The CD4/CD8 ratio of BALF was 1.44. The BALF culture, cytology, viral isolation and *Pneumocystis jirovecii* polymerase chain reaction analysis were negative. Histopathological findings of TBLB showed patchy processes characterized primarily by organizing pneumonia involving alveolar ducts and alveoli with bronchiolar intraluminal polyps (Fig. 2). Sputum, blood,

Table 1

Previously reported UC patients with mesalazine-induced lung injury (reports written in English or Japanese).

No.	Age	Sex	5-ASA: daily dose/duration	Initial SpO ₂ (%) or PaO ₂ (mmHg)	Device for oxygenation	BALF (%)				Diagnosis	Steroid treatment	Outcome	Author/year
						Mac	Lym	Neu	Eos				
1	54	F	0.75g/17 days	N/A	N/A	63	35	0.5	1.5	HP	No	Recovery	V Le Gros 1991 [1]
2	67	M	1g/10 days	N/A	N/A	N/A	N/A	N/A	N/A	IP	Yes	Recovery	Welte T 1991 [2]
3	64	F	3.6g/2 years	65 mmHg	No	-	-	-	-	IP	No	Recovery	Reinoso AM 1992 [3]
4	30	F	1.6g/8 months	N/A	N/A	-	-	-	-	EP	No	Recovery	Honeybourne D 1994 [4]
5	32	F	4g/9 months	76 mmHg	No	N/A	N/A	N/A	N/A	IP	Yes	Recovery	Bitton A 1996 [5]
6	60	M	N/A/4 weeks	N/A	N/A	80	8	2	10	IP	No	Recovery	Lázaro TM 1997 [6]
7	72	F	1.6g/1 month	N/A	N/A	N/A	N/A	N/A	N/A	IP	Yes	Recovery	Sesin PG 1998 [7]
8	56	M	2.25g/1 month	78.4 mmHg	No	92	5	2	1	IP	Yes	Recovery	Ogino H 1998 [8]
9	35	F	1.5g/40 days	N/A	N/A	43.5	49	0	7.5	EP	No	Recovery	Tanigawa K 1999 [9]
10	29	f	1g/2 days	N/A	N/A	-	-	-	-	IP	Yes	Recovery	Guslandi M 1999 [10]
11	18	F	1.6g/3 years	65 mmHg ^a	Nasal cannula	N/A	N/A	N/A	N/A	OP	Yes	Recovery	Haralambou G 2001 [11]
12	70	F	2.4g/3 months	49 mmHg	N/A	0	60	0	0	IP	No	Recovery	Sossai P 2001 [12]
13	53	F	N/A/N/A	N/A	N/A	N/A	N/A	N/A	79	EP	Yes	Recovery	Saltzman K 2001 [13]
14	29	F	3.6g/8 month	53 mmHg	N/A	-	-	-	-	IP	Yes	Recovery	Foster RA 2003 [14]
15	30	F	4.8g/2 years	97%	N/A	57	0	43	0	IP	Yes	Recovery	Foster RA 2003 [14]
16	30	M	2.25g/1 month	91.7 mmHg	No	7	11	0	82	EP	Yes	Recovery	Hakoda Y 2004 [15]
17	50	F	-/1 month	66.8 mmHg	No	18	58	4	20	EP	No	Recovery	Shimizu T 2009 [16]
18	26	M	2.25g/1 month	55.1 mmHg	N/A	3.5	13.5	16	67	EP	Yes	Recovery	Machida H 2011 [17]
19	27	F	1.5g/3 weeks	79.8 mmHg	No	-	-	-	-	IP	No	Recovery	Machida H 2011 [17]
20	52	M	1.5-4g/7.5 years	98%	No	36	18	35	12	OP	No	Recovery	Shindoh Y 2011 [18]
21	30	F	1g/19 days	N/A	N/A	73.2	0	19.6	1.6	EP	Yes	Recovery	Kim HJ 2013 [19]
22	65	M	1.2g/2 weeks	70.7 mmHg ^b	Intubation	N/A	N/A	N/A	N/A	IP	Yes	Recovery	Abraham A 2013 [20]
23	48	F	N/A	N/A	N/A	23	7	22.5	47.5	EP	No	Recovery	Inoue M 2014 [21]
24	15	F	2.25g/4 weeks	N/A	N/A	-	-	-	-	EP	No	Recovery	Inoue M 2014 [21]
25	50	F	3.6g/5 weeks	N/A	N/A	-	-	-	-	EP	No	Recovery	Inoue M 2014 [21]
26	26	F	2g/8 months	99%	No	-	-	-	-	OP	Yes	Recovery	Kacprzak A 2014 [22]
27	31	M	N/A/5 years	97%	No	80.5	13.5	5.5	0.5	OP	Yes	Recovery	Kacprzak A 2014 [22]
28	65	F	3g/2.5 years	96%	No	58.1	39.4	2.5	0	IP	Yes	Recovery	Kacprzak A 2014 [22]
29	74	M	3g/1 month	87.7 mmHg	No	47.4	3.8	9.4	39.4	EP	Yes	Recovery	Kikuchi R 2015 [23]
30	53	M	3.6g/11 days	95%	No	2	3	0	95	EP	Yes	Recovery	Kobari T 2018 [24]
31	58	F	2.4g/6 weeks	70.8 mmHg ^c	NPPV	6.8	44	16	32.4	OP	Yes	Recovery	Our case

UC = ulcerative colitis; 5-ASA = 5-aminosalicylic acid; BALF = bronchoalveolar lavage fluid; Mac = macrophage; Lym = lymphocyte; Neu = neutrophil; Eos = eosinophil; IP = interstitial pneumonia; EP = eosinophilic pneumonia; OP = organizing pneumonia; NPPV = non-invasive positive pressure ventilation; N/A = no data available.

^a 5L/min oxygen via nasal cannula.

^b 2L/min oxygen via nasal cannula.

^c 4L/min oxygen via nasal cannula.

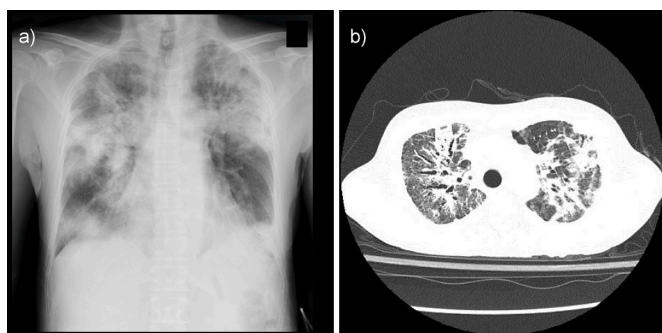


Fig. 1. Chest radiograph and computed tomography (CT) on admission. a): Chest radiograph demonstrates diffuse infiltrative shadows in the bilateral lung fields. b): Chest CT shows bilateral and asymmetric air space consolidation and ground-glass opacity with a peribronchial and subpleural distribution.

and urine cultures were negative. Extensive blood tests including paired complement fixation test and hemagglutination inhibition test for respiratory associated viruses (respiratory syncytial virus; adenovirus; seasonal influenza A and B; cytomegalovirus; parainfluenza virus 1–3) were all negative. Drug-induced lymphocyte stimulation test (DLST) for mesalazine was negative. Considering these findings and the clinical course, we suspected organizing pneumonia of UC or mesalazine-

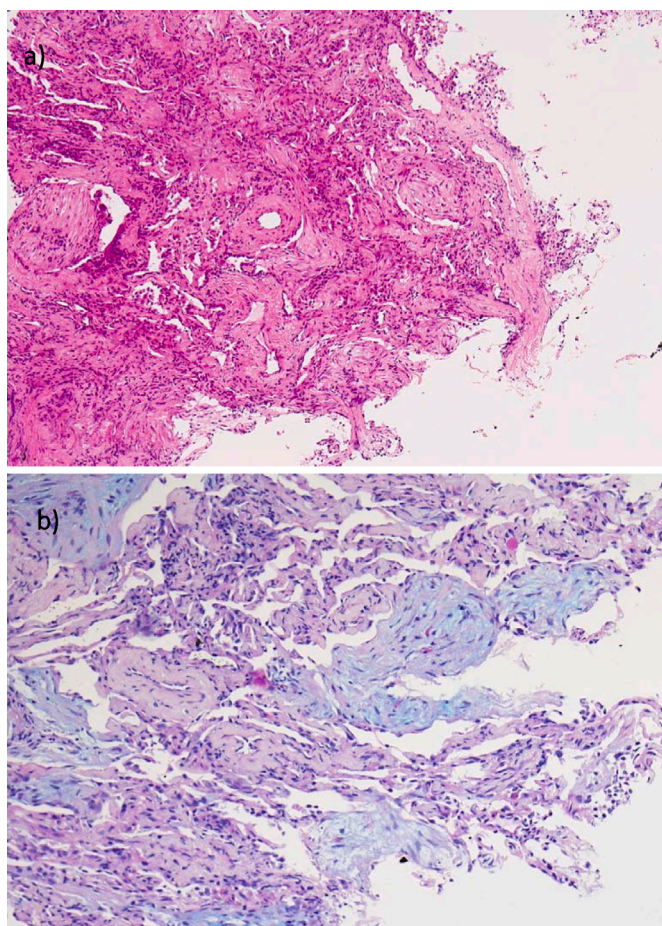


Fig. 2. Histopathological findings of lung tissue by transbronchial lung biopsy. Patchy process characterized primarily by organizing pneumonia involving alveolar ducts and alveoli with bronchiolar intraluminal polyps. a): haematoxylin-eosin stain (original magnification $\times 10$); b): Alcian-blue and periodic acid-Schiff stain ($\times 20$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

induced lung injury.

On the day of admission, mesalazine was discontinued and the patient was treated with corticosteroid therapy (intravenous methylprednisolone pulse therapy [1000 mg per day for 3 days] followed by low dose oral prednisolone). NPPV was immediately initiated to treat severe respiratory failure. Initial management of NPPV was positive end-expiratory pressure (PEEP) 5cmH₂O with inspired fraction of oxygen (FiO₂) of 0.60. According to the Berlin definition of ARDS, she had mild ARDS: partial pressure of oxygen/FiO₂ [PaO₂/FiO₂] with PEEP 5cmH₂O was 206. Afterwards, oxygenation gradually improved and PaO₂/FiO₂ with PEEP 5 cmH₂O was 355 on day 6. Follow up CT scan showed significant improvement (Fig. 3). NPPV was discontinued and from the patient no longer required oxygen therapy on day 11 (Fig. 4). Eventually, her respiratory status had fully recovered and she was discharged from the hospital on day 25. After resolution, her UC also subsided and no medication has been needed for 3 years. She has also been free from relapse of lung injury.

The diagnostic criteria of DLI are shown in Table 2 [25,26]. We diagnosed her with mesalazine-induced lung injury because she met criteria (1) to (4) starting from the past.

3. Discussion

We present a case of mesalazine-induced lung injury with severe respiratory failure and a confirmed histological pattern of organizing pneumonia that was successfully treated with discontinuation of mesalazine and provision of steroid pulse therapy and NPPV. Almost all UC patients with mesalazine-induced lung injury in the literature review showed mild or no respiratory failure, which was improved only by discontinuation of the drug or administration of low-dose corticosteroids [1–24] (Table 1).

There is a tendency to treat most patients with DLI with systemic corticosteroids, although there is no clear evidence to support this approach. The Japanese consensus statement for the treatment of DLI [25] proposes methylprednisolone pulse therapy (500–1000 mg per day for 3 days) followed by 0.5–1.0 mg/kg/day of prednisolone for patients with severe respiratory failure (PaO₂ < 60 Torr or PaO₂/FiO₂ < 300). In the present case, we treated the patient with methylprednisolone pulse therapy followed by low dose prednisolone because of severe respiratory failure (PaO₂/FiO₂ = 206).

We used steroid pulse therapy in treating this patient. Steroid pulse may lead to an immunosuppressed condition, and Hilbert et al. [27] demonstrated that in selected immunosuppressed patients with pneumonitis and acute respiratory failure, early initiation of NPPV was associated with significant reductions in the rates of endotracheal intubation and serious complications. We started to use NPPV on the day of admission. Yokoyama et al. [28] also reported that early intervention with NPPV was beneficial for the management of patients with rapidly progressive interstitial pneumonia in a subject group in which one third of all subjects (32%) had DLI.

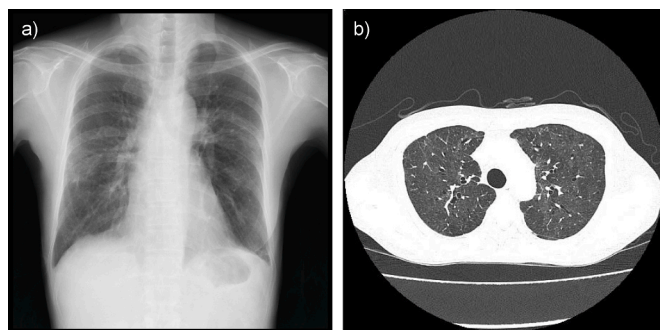


Fig. 3. Chest radiograph and computed tomography on day 18. a) and b): Almost fully recovered from the ground-glass opacities and infiltration.

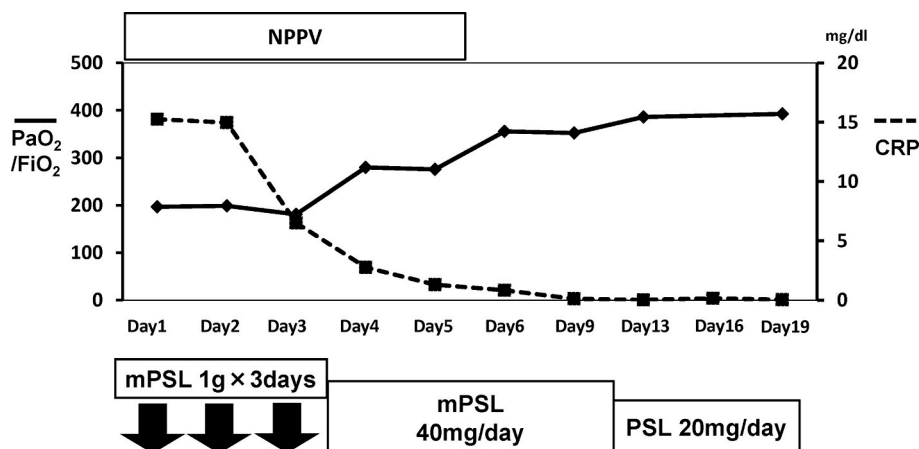


Fig. 4. Clinical course of the patient. mPSL, methylprednisolone; PSL, prednisolone; NPPV, non-invasive positive pressure ventilation; CRP, c-reactive protein.

Table 2

Diagnostic criteria for DLI [25,26].

1. History of ingestion of a drug that is known to induce lung injury.
2. The clinical manifestations have been reported to be induced by a drug.
3. Other causes of the clinical manifestations could be ruled out.
4. Improvement of the clinical manifestations after drug discontinuation.
5. Exacerbation of the clinical manifestations after resuming drug administration.

Whether UC is related to lung disease is important. Camus et al. [29] stated that 70% of patients who had pulmonary involvement associated with intestinal bowel disease experienced an additional extraintestinal manifestation in combination with their lung involvement. In addition, the symptoms related to pulmonary involvement of UC paralleled the activity of the intestinal disease [30]. In the present case, there was no evidence of the progression of UC, so the disease activity of the pulmonary infiltration was not considered to parallel to the activity of UC. Therefore, we thought that the probability of pulmonary involvement from UC was low in the present case.

The time from drug exposure to diagnosis has varied in reports of mesalazine-induced lung injury (Table 1). In two previously reported cases of mesalazine-induced lung injury with severe respiratory failure, DLI occurred after 2 weeks or 3 years of drug exposure [11,20]. In the present case, DLI developed after 6 weeks. The relationship between time of use of mesalazine and lung injury is unclear from these reports and the present case. Further study is needed on the relationship between time from drug exposure and severity of mesalazine-induced lung injury.

The present case showed elevated populations of lymphocytes, eosinophils, and neutrophils in BALF and negative findings for respiratory infection. Although an elevated eosinophil count was observed in BALF, histological findings showed only mild inflammation. While examination of BALF may not lead to a definitive diagnosis of DLI, BALF findings are potentially useful in ruling out other conditions, such as infection [25]. In previous reports (Table 1), BALF findings can be grouped into three types: elevated eosinophils, elevated lymphocytes, and elevated levels of three types of leucocytes, but it is unclear whether fractional differences in them are associated with the severity of mesalazine-induced lung injury. Additionally, BALF cellular findings in any case are non-specific. Further study is needed on the difference between these fractions and the severity of mesalazine-induced lung injury.

In conclusion, we present a case of mesalazine-induced lung injury with severe respiratory failure, which was improved by corticosteroid therapy and NPPV. This is the first report describing in detail the BAL of mesalazine-induced lung injury in UC and NPPV as respiratory management. It should be noted that severe cases of mesalazine-induced

lung injury are rare.

Financial disclosure and conflicts of interest

All of the authors declare that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. Dr. Kondoh reports personal fees from Asahi Kasei Pharma Corp.; personal fees from Boehringer Ingelheim Co., Ltd., personal fees from Janssen Pharmaceutical K.K., personal fees from Eisai inc., personal fees from KYORIN Pharmaceutical Co., Ltd., personal fees from Mitsubishi Tanabe Pharma, personal fees from Novartis Pharma K.K., personal fees from Shionogi & Co., outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2020.101157>.

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