Case Report

Course of matrix metalloproteinase-1 and pulmonary oxygenation in acute respiratory distress syndrome caused by oral ingestion of large doses of oxadiazon/butachlor emulsion: a case report

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Background: We treated a patient who developed acute respiratory distress syndrome following ingestion of oxadiazon/butachlor emulsion. In this case, we continuously measured matrix metalloproteinase-1 level, an enzyme that reduces the extracellular matrix in the lungs, and tissue inhibitors of metalloproteinase-1.

Case Presentation: A 50-year-old woman attempted suicide by ingesting approximately 300 mL of oxadiazon/butachlor emulsion. Respiratory disorders were observed upon admission, therefore tracheal intubation was performed, followed by artificial respiratory management (ventilator support). After that, her condition became complicated by acute respiratory distress syndrome, but it improved with intensive care management. Matrix metalloproteinase-1 level showed a course opposite to the partial pressure of arterial oxygen/percentage of inspired oxygen ratio, whereas the matrix metalloproteinase-1/tissue inhibitors of metalloproteinase-1 ratio changed in parallel with the partial pressure of arterial oxygen/percentage of inspired oxygen ratio.

Conclusion: The relationship between matrix metalloproteinase-1 and tissue inhibitors of metalloproteinase-1 was presumed to be important for the development of acute respiratory distress syndrome.

Key words: Acute respiratory distress syndrome, butachlor, matrix metalloproteinase, oxadiazon, tissue inhibitors of metalloproteinase, xylene

INTRODUCTION

EXTRACELLULAR MATRIX (ECM) is a substance surrounding cells in tissues; is composed of collagen, proteoglycan, and structural glycoprotein, among others; and is strongly involved in maintaining cell functions such as cell growth, differentiation, and adhesion as well as tissue support.[1,2] Degradation of ECM in the lungs involves both proteases produced locally in the lungs and elastase derived from neutrophils that migrate to the lungs.[3] Matrix metalloproteinase (MMP) is the most important group of enzymes involved in ECM degradation, and its activity is strictly controlled by its specific inhibitor, that is, tissue inhibitors of metalloproteinase (TIMP). Disruption of the quantitative balance between MMP and TIMP has been suggested to cause tissue destruction.[4,5] We also reported the association between MMPs and TIMPs in patients with respiratory disorders.[6,7] Oxadiazon/butachlor (Delcut, Nissan Chemical Corporation, Tokyo, Japan) emulsion is a kind of acid amide herbicide that has been widely used for many years in Japan. Oxadiazon has relatively low toxicity; however, ingesting butachlor causes nausea, vomiting, abdominal pain, diarrhea, methemoglobinemia, and hemoglobinuria among others.

In this case report, we investigated the relationship between blood MMP-1 and pulmonary oxygenation in a patient with acute respiratory distress syndrome (ARDS) caused by ingesting oxadiazon/butachloremulsion.

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CASE REPORT

CASE: A WOMAN in her 50s.

Family history: Unremarkable.

Past history: Unremarkable.

Present illness: Around noon, on June 18, in 20XX, the patient was found unconscious in her car. Approximately 35 min after the discovery, the patient was transported to our hospital by ambulance. A bottle of oxadiazon/butachlor emulsion (500 mL) was found in her car, with approximately 200 mL remaining content. The patient left home at 6 am, but the exact time of oxadiazon/butachlor emulsion ingestion was unknown.

Upon hospital admission, her blood pressure was 88/54 mmHg, and she was in a shock state with a Glasgow Coma Scale of 4 points (Eye: 1, Voice: 1, Movement: 2). Her respiratory condition was poor; therefore, tracheal intubation was performed immediately and she was put on a ventilator. No obvious oxadiazon/butachlor emulsion aspiration was observed during the bronchoscopic examination. Echocardiography did not reveal any abnormal findings that suggested heart failure. In addition to respiratory and circulatory disorders, methemoglobinemia, hemoglobinuria, liver, and kidney disorders were observed. Blood test results upon admission are presented in Table 1. The Acute Physiology and Chronic Health Evaluation II score and the Sequential Organ Failure Assessment score were 40 and 19 points, respectively. Chest computed tomography showed mild infiltrates in both lungs (Fig. 1). Chest radiographs showed infiltrative shadows on both lungs (Fig. 2A); besides, her PaO_2/FiO_2 (partial pressure of arterial oxygen/percentage of inspired oxygen [P/F]) ratio was 112 and heart failure was negative on echocardiography. Based on these findings, the patient was diagnosed with ARDS. Her acute phase disseminated intravascular coagulation (DIC) score was 2 points. Shock treatment was initiated with 10 μg/kg/min of dopamine and 5 μg/kg/min of dobutamine in addition to fluid replacement, and the dose was reduced as appropriate. Haptoglobin 4,000 U was administered once for hemoglobinuria. In addition, proteolytic enzyme inhibitors, ulinastatin and nafamostat, were administered, and a continuous administration of a steroid (methylprednisolone 1 g/day) was started (Fig. 3). For acute kidney injury, hemodialysis was started on the third day after admission and continued until the ninth day after admission according to symptoms. MMP-1 was high on admission but rapidly dropped on the third day; however, TIMP-1 remained high (Fig. 3). Tumor necrosis factor-α (TNF-α) was below the measurement limit during the entire course. The P/F ratio rapidly increased from the third day after admission and she

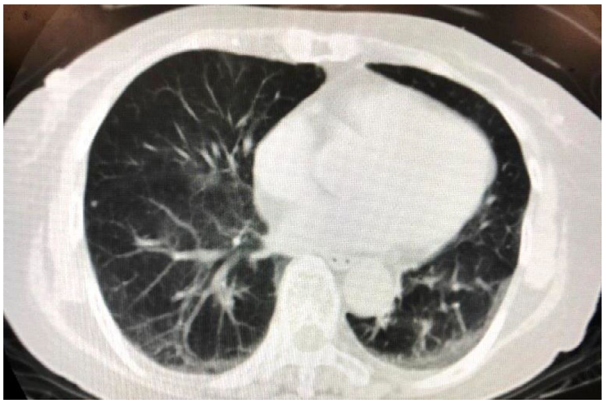

Fig. 1. Chest computed tomography scan on admission. A slight infiltrative shadow was observed on both sides.

Table 1. Test results at the time of visit

Body temperature	35.8°C	Aspartate transaminase	244 IU/L
Mean blood pressure	65 mmHg	Alanine aminotransferase	238 IU/L
Heart rate	76/min	Total bilirubin	4.8 mg/dL
Respiratory rate	28/min	Blood urea nitrogen	44.5 mg/dL
pH	7.14	Creatinine	2.2 mg/dL
Methemoglobin	13.8%	C-reactive protein	24.9 mg/dL
Sodium	138 mmol/L	Platelets	18.2×10^4/mL
Potassium	4.7 mmol/L	Prothrombin time-international normalized ratio	1.09
Chloride	99 mmol/L	Fibrinogen degradation product	14.5 μg/mL
Hematocrit	50.1 %	Fibrinogen	511.5 mg/mL
White blood cells	35.1×10^3/mL	Antithrombin III	88%

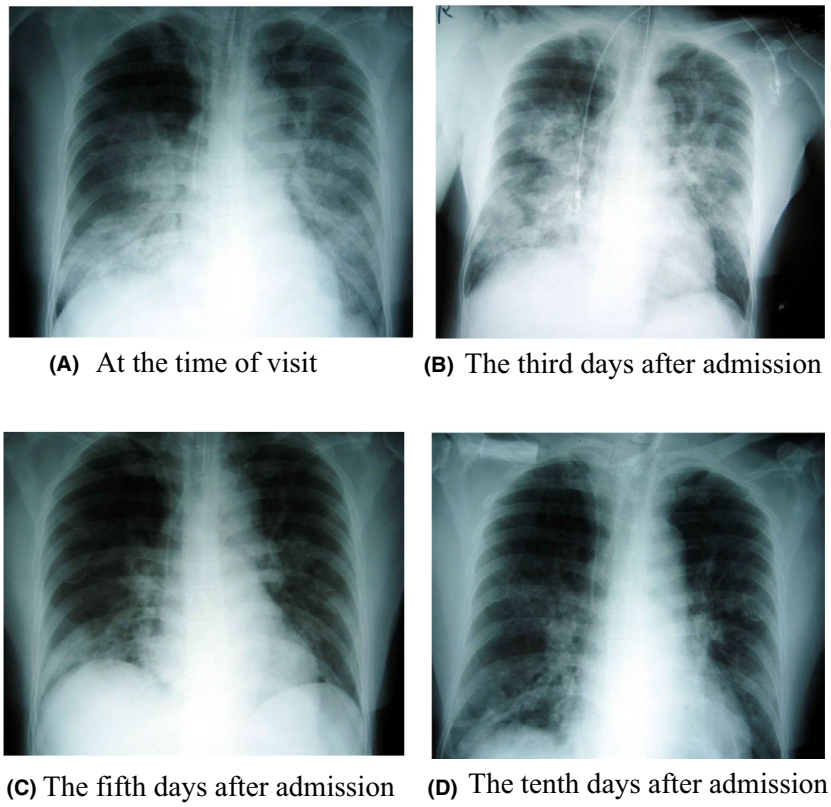

Fig. 2. Changes in chest radiographs. A, X-ray photograph at the time of visit. A slight infiltrative shadow is seen on both sides. B, X-ray photograph on the third day after hospitalization. Although the infiltrative shadows on both sides were exacerbated, the respiratory condition gradually improved from this day. C, X-ray photograph on the fifth day after hospitalization. The infiltration shadow gradually improved. D, X-ray photograph taken 10 days after admission. The infiltration shadow has disappeared.

was extubated the tenth day after admission (Fig. 3). Chest radiographs worsened on the second day after admission, but the infiltrates on both lungs gradually disappeared with an improved respiratory status. Multiple organ failure (MOF) also improved on the ninth day after admission, and she was finally discharged on the 75th day. Figure 3 shows the course of the P/F ratio, MMP-1 value, and TIMP-1/MMP-1 ratio.

The American–European Consensus Conference on ARDS criteria[8] were used to diagnose ARDS. The P/F ratio was used to evaluate the lung oxygenation ability. The acute-phase DIC score[9] was used to diagnose DIC. Blood samples were continuously obtained to measure MMP-1, TIMP-1, and TNF-α since admission, and the serum was separated and stored at −80°C until measurement. Both MMP-1 and TIMP-1 were measured using an enzyme-linked immunosorbent assay (ELISA; Amersham Biosciences, Ltd., Buckinghamshire, UK). TNF-α was also measured by an ELISA (Medogenix, Fleurus, Belgium).

DISCUSSION

OXADIAZON/BUTACHLOR emulsion consists of 8% oxadiazon, 12% butachlor, approximately 70% xylene, and 9% surfactant. Based on our literature review, respiratory disorders caused by oxadiazon/butachlor emulsion ingestion have not yet been reported, and the component that caused this condition is unknown. Although butachlor may cause methemoglobinemia and hemoglobinuria, no studies have reported respiratory disorders or MOF. When a large amount of xylene enters the body, renal dysfunction, liver dysfunction, memory disorder, and consciousness disorder, among others, may occur in severe cases. In addition, cases of severe respiratory disorder mainly caused by xylene ingestion have already been reported.[10] Treatments for oxadiazon/butachlor emulsion ingestion are as follows: intravenous injection of 0.1% methylene blue for methemoglobinemia and haptoglobin for hemoglobinuria. In addition, standard effective treatment for xylene has not yet been clearly established; thus, targeted therapy will be

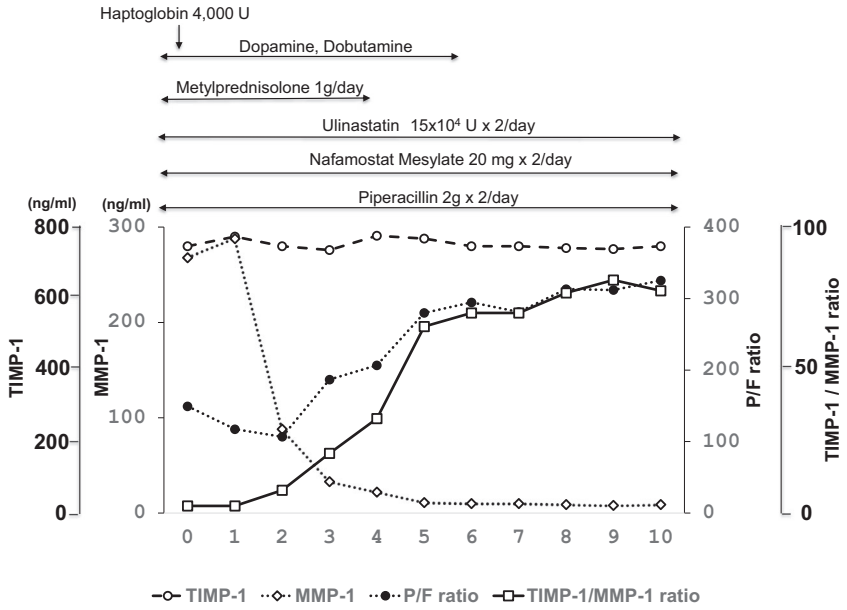

Fig. 3. Clinical course and transition of each marker. From the second day after admission, MMP-1 decreased rapidly. Along with that, the respiratory condition gradually improved. The TIMP-1/MMP-1 ratio changed in parallel with the P/F ratio. MMP-1, matrix metalloproteinase-1; TIMP-1, tissue inhibitors of metalloproteinase-1; P/F, partial pressure of arterial oxygen/percentage of inspired oxygen.

administrated according to symptoms. When performing gastric lavage, the risk of chemical pneumonia due to aspiration remains high; therefore, it must be performed after tracheal intubation. Gastric lavage was performed after tracheal intubation in this case. Methemoglobinemia was not severe, so 0.1% methylene blue was omitted. Haptoglobin 4,000 U was administered for hemoglobinuria, which led to a visually normal urine on the second day of hospital stay. In addition to the vasopressor administered for shock, proteolytic enzyme inhibitors, ulinastatin and nafamostat, were administered. These effects are considered to enable a rapid recovery from MOF.

MMPs, such as MMP-1, MMP-2, MMP-7, and MMP-9, are thought to be involved in ARDS development. In our previous studies, we considered MMP-1 as the best determinant for ARDS pathology.[6,7] Therefore, we also measured the MMP-1 in this case. The P/F ratio and MMP-1 showed opposite trends, whereas TIMP-1 hardly fluctuated and the P/F ratio and the TIMP-1/MMP-1 ratio showed a parallel transition. Whether MMP-1 is directly involved in ARDS development remains controversial but suggests that MMP-1 and the TIMP-1/MMP-1 ratio may be important indicators in assessing respiratory disorders. Some reports revealed that MMPs and TIMPs are involved in lung fibrosis; therefore, we would like to investigate further whether these markers are prognostic indicators of ARDS. The component of oxadiazon/butachlor emulsion that promotes MMP-1 production should also be identified. ARDS may rapidly develop if oxadiazon/butachlor emulsion is ingested in large doses; thus, caution is required in such cases.

CONCLUSION

WE REPORTED A case of ARDS and MOF caused by oral ingestion of large doses of oxadiazon/butachlor emulsion. The relationship between MMP-1 and TIMP-1 was presumed to be important for the development of ARDS.

AUTHORS' CONTRIBUTIONS

GT TREATED THIS case and performed redaction and correction of the manuscript. HY and MT, DY, and YF treated this case and collected blood samples and data. YI and SE assisted with clinical management of the case and correction of the manuscript. All authors read and approved the final manuscript.

CONSENT FOR PUBLICATION

WRITTEN INFORMED CONSENT was obtained from the patient for publication of this case report

and accompanying images. A copy of the written consent is available for review by the editor of this journal.

DISCLOSURE

Approval of the research protocol: Not applicable.
Informed Consent: The measurement was approved by the patient's family.
Registry and the Registration No. of the study/Trial: Not applicable.
Animal Studies: Not applicable.
Conflict of Interest: None declared.

DATA AVAILABILITY STATEMENT

The data generated and analyzed in this study are included in this published article. The original data sets used for this study are not publicly available due to the existing regulation, and only can be shared upon the approval of the directors of the corresponding hospitals.

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