CASE REPORT

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Type B insulin-resistance syndrome presenting as autoimmune hypoglycemia, associated with systemic lupus erythematosus and interstitial lung disease

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We describe an unusual case of systemic lupus erythematosus with pulmonary manifestations presenting as hypoglycemia due to anti-insulin receptor antibodies. A 38-year-old female suffered an episode of unconsciousness and was admitted to hospital where her blood glucose was found to be 18 mg/dL. During the hypoglycemic episode, her serum insulin level was inappropriately high (2,207.1 pmol/L; normal range, 18 to 173) and C-peptide level was elevated (1.7 nmol/L; normal range, 0.37 to 1.47). Further blood tests revealed the presence of antinuclear antibodies, anti-double-stranded DNA antibodies, and anti-Ro/SSA, anti-La/SSB, anti-ribonucleoprotein, and anti-insulin receptor antibodies. A computed tomography scan of the abdomen, aimed at tumor localization, such as an insulinoma, instead revealed ground-glass opacities in both lower lungs, and no abnormal finding in the abdomen. For a definitive diagnosis of the lung lesion, video-associated thoracoscopic surgery was performed and histopathological findings showed a pattern of fibrotic non-specific interstitial pneumonia.

Keywords: Autoimmune hypoglycemia; Lupus erythematosus, systemic; Lung diseases, interstitial

INTRODUCTION

Autoimmune hypoglycemia is generally classified into two types. One is insulin autoimmune syndrome and the other is type B insulin-resistance syndrome, which are characterized by the presence of autoantibodies directed to endogenous insulin and to the cell-surface insulin receptor, respectively [1]. Only a small minority of patients with type B insulin-resistance syndrome experience hypoglycemic manifestations; most of them present with severe hyperglycemia associated with extreme insulin resistance [2]. A common feature of type B insulin-resistance syndrome is the co-occurrence of autoimmune disorders, such as systemic lupus erythematosus (SLE) [2]. We report here a very rare case of type B insulin-resistance syndrome, which presented with hypoglycemia and was associated with SLE and pulmonary manifestations.

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CASE REPORT

A 38-year-old Korean woman suffered an episode of unconsciousness and was transferred to an emergency center where her blood glucose was found to be 18 mg/dL. She recovered her senses after intravenous infusion of distilled water containing 50% dextrose. She had no relevant medical or family history except the development of the skin rashes after sunlight exposure. The patient denied any use of exogenous insulin or oral hypoglycemic agents and she was not employed in a health-related profession. Her vital signs were as follows: blood pressure, 120/70 mmHg, heart rate, 75/min, and body temperature, 36.7°C. A physical examination was unremarkable other than the presence of fixed erythematous plaques on her cheeks. During the hypoglycemic episode, her serum insulin level was very high (2,207.1 pmol/L; normal range, 18 to 173) and the C-peptide level was elevated (1.7 nmol/L; normal range, 0.37 to 1.47). The patient underwent a diagnostic fasting test. After 4 hours of fasting, she developed symptomatic hypoglycemia, with a glucose level of 32 mg/dL, accompanied by an inappropriately high serum insulin level of 1,430.1 pmol/L and a C-peptide level of 1.6 nmol/L. For the differential diagnosis of hypoglycemia associated with unsuppressed insulin level, a computed tomography (CT) scan of the abdomen was performed, but it failed to localize any pancreatic tumor, such as an insulinoma. Instead, the abdominal CT revealed ground-glass opacities and intralobular reticular pattern densities on both lower-lung fields (Fig. 1A), although there was no abnormal finding on her chest radiographs (Fig. 1B) and she did not complain of respiratory symptoms, such as dyspnea, cough, sputum production, or chest tightness. An additional high-resolution CT (HRCT) scan showed the same findings, suggesting interstitial lung disease (ILD) (Fig. 1C and 1D). Further biochemical and serologic studies showed following abnormal values: positive titer for antinuclear antibodies, anti-double-stranded DNA (dsDNA) antibodies, anti SS-A/SS-B antibodies, and anti-ribonucleoprotein antibodies, erythrocyte sedimentation rate 85 mm/hr, C3 0.821 g/dL, and C4 0.096 g/dL. Other tests, including complete blood count, hepatic and renal function, thyroid function, urinalysis, anti-phospholipid antibody, and anti-insulin antibody were unremarkable. Considering all these facts, the presence of type B insulin-resistance syndrome associated with SLE was suggested, and a confirmed diagnosis was made after a positive anti-insulin receptor antibody radioreceptor assay. For a definitive diagnosis of the lung lesions, video-associated thoracoscopic surgery was performed and the histopathological findings showed a pattern of fibrotic non-specific interstitial pneumonia. The patient was referred to the Department of Rheumatology and Immunosuppressive Therapy, and a combination of prednisolone 30 mg/day, hydroxychloroquine 300 mg/day, and azathioprine 50 mg/day was started. She has had no further recurrence of hypoglycemia, and the dose of prednisolone has since then been decreased gradually to 5 mg/day during her outpatient follow-up.

DISCUSSION

We report a very unusual case of type B insulin-resistance syndrome presenting with an autoimmune form of hypoglycemia, which was associated with SLE and accompanied by asymptomatic ILD.

There are two types of insulin-resistance syndrome, types A and B [3]. Type B insulin-resistance syndrome is characterized by presence of anti-insulin receptor antibodies, which impair the binding of insulin to its receptor and cause insulin resistance. On the other hand, insulin resistance in the clinically similar type A syndrome results from a primary structural defect in the insulin receptor, due to a genetic mutation [3,4]. Unlike our patient, the clinical manifestations observed in patients with type B insulin-resistance syndrome consist most commonly of hyperglycemia associated with extreme insulin resistance because of the insulin receptor-antagonizing action of the autoantibodies [2]. Less commonly, anti-insulin receptor antibodies may have agonist activity, resulting in hypoglycemia. This phenomenon appears to be caused by the binding of autoantibodies to insulin receptors, which inhibits the degradation of insulin and results in hyperinsulinemia, followed by subsequent hypoglycemia. Lupsa et al. [5], who followed 34 patients with type B insulin-resistance syndrome who were admitted to the Clinical Research Center of the National Institutes of Health between January 1973 and July 2008 reported

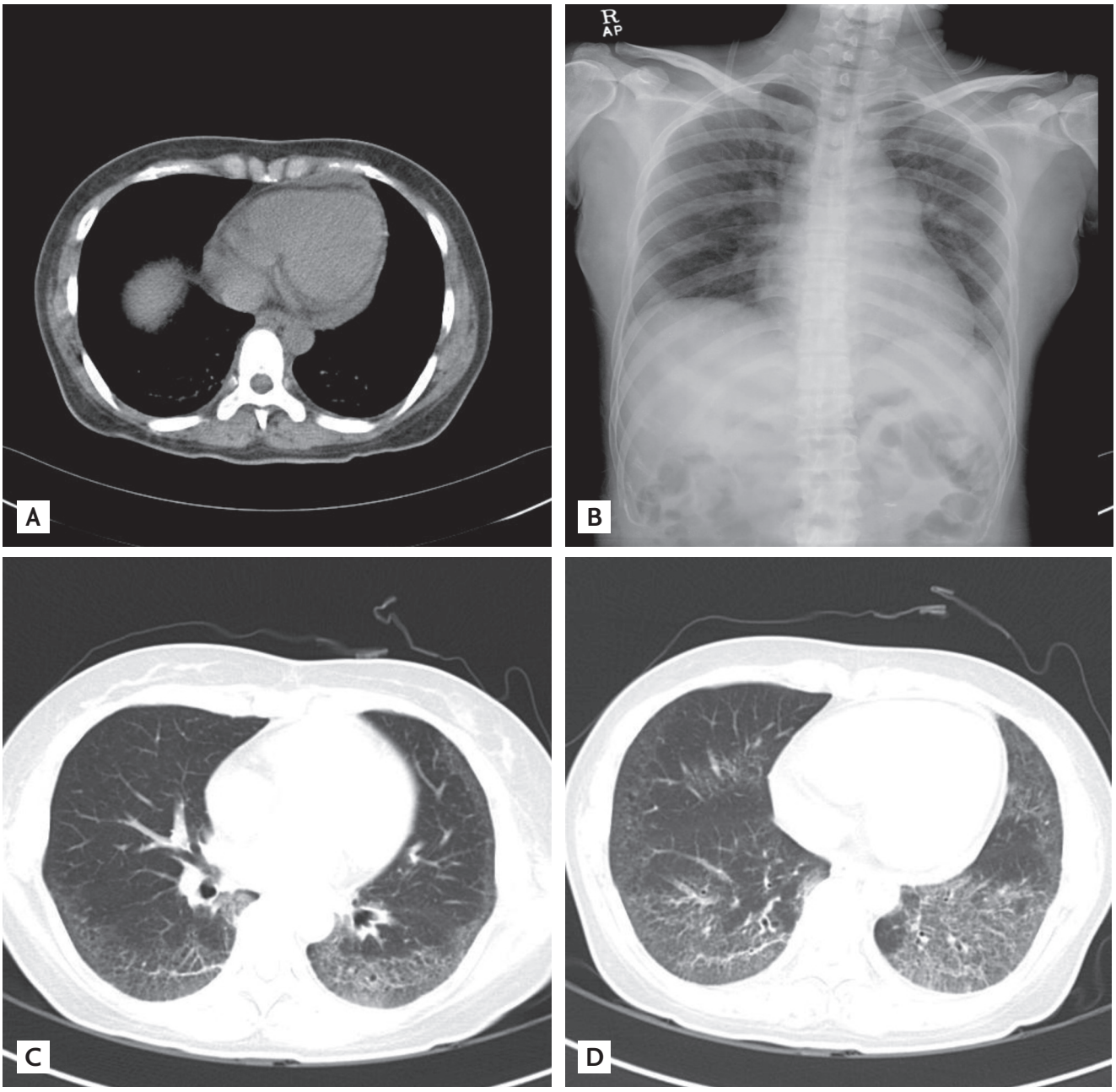

Figure 1. (A) Abdominal computed tomography (CT) revealed mixed reticular and ground-glass opacities in both lower-lung zones. (B) Chest radiograph on admission showed no specific abnormality. (C, D) High-resolution CT showed intralobular reticular and ground-glass opacities in both lower lobes, the right-middle lobe, and the left lingular segment. Band-like thickened intralobular septa were also observed.

that 24% (8/34) manifested some form of hypoglycemia during the course of the illness. Hypoglycemia may occur during the fasting or postprandial states, usually after a preceding period of hyperglycemia. A few patients with type B insulin-resistance syndrome may initially present with spontaneous hypoglycemia and never manifest hyperglycemia. To our knowledge, only two cases of type B insulin-resistance syndrome have been reported in Korea. As in our patient, recurrent fasting hypoglycemia without hyperglycemic episodes

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was also seen in the previous reports [6,7].

A common feature of type B insulin-resistance syndrome is the coexistence of autoimmune disorders, such as Hashimoto's thyroiditis, primary biliary cirrhosis, systemic sclerosis, Sjögren's syndrome, and SLE, at presentation. Arioglu et al. [2] reported that the most common underlying autoimmune disorder in their series of 24 patients was SLE. In our case, the patient had malar rashes on her cheeks and skin photosensitivity before admission. Although she had no other typical symptoms of SLE, biochemical and serologic studies showed the presence of antinuclear antibodies and anti-dsDNA antibodies. On the basis of this evidence, we diagnosed her with SLE. However, the severity of type B insulin resistance may not be correlated with lupus activity. Furthermore, the mechanisms responsible for the development of anti-insulin-receptor antibodies in these coexisting autoimmune disorders remains unknown.

SLE is an autoimmune disease characterized by the production of various autoantibodies and can cause alterations in components of connective tissue in multiple organs, including the lung. Pleuritis is the most common pleuropulmonary manifestation of SLE and chronic ILD is a rare complication [8]. Patients usually have persistent dyspnea on exertion, occasional pleuritic chest pain, non-productive cough, and bibasilar crackles on lung auscultation. However, the onset of ILD is insidious in most cases; early in the course of the disease, patients may be asymptomatic and chest radiographs may be normal [9]. Pulmonary function tests may reveal a restrictive defect or loss of lung volume and a reduction in the diffusion capacity for carbon monoxide. Linear thickened interlobular septa and parenchymal bands are the most common HRCT findings, but these are non-specific [8]. A lung biopsy may help to exclude other conditions. On lung biopsy, the most common histological patterns are those of cellular, fibrotic or mixed non-specific interstitial pneumonia [10]. In our case, we found no other abnormality on the first physical examination at the emergency center. However, careful re-examination revealed bibasilar fine crackles on lung auscultation after the detection of lung lesion on the CT scan.

We report this extremely rare case of type B insulin-resistance syndrome presenting with hypoglycemia induced by anti-insulin-receptor antibodies, associated with SLE and complicated with ILD. We learned two lessons from this case. It is important that the presence of antibodies to insulin and its receptor should be considered in any patient who presents with hypoglycemia accompanied by an inappropriately high level of insulin, especially in conjunction with autoimmune features. Furthermore, we should remember that among the myriad diagnostic tests available, a careful physical examination remains a priority.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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