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CASE REPORT

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Serum immunogloblins might be useful predictors of immune-related adverse events after immune checkpoint inhibitor usage in lung cancer

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Abstract

We herein report a 79-year-old woman who underwent surgery had recurred non-small cell lung cancer and developed irAEs following ICI treatment. During ICI treatment, we conducted monthly measurements of the serum antibody levels in this patient, including those which were both tumor- (anti-p53 antibody) and nonspecific (immunoglobulins). Anti-p53 antibodies and IgM had not increased during ICI treatment, but the serum levels of IgG and IgA had gradually increased before the occurrence of irAEs. These results suggest that monitoring serum immunoglobulin levels might enable the early detection of ICI-induced immune responses in patients with lung cancer.

KEYWORDS

humoral immune response, immune checkpoint inhibitor, immune related adverse events, lung cancer

INTRODUCTION

Immune checkpoint inhibitors (ICIs) that block the programmed death 1 (PD-L1)/programmed death ligand 1 pathways are effective in about 20% of lung cancer cases.[1,2] However, immune-related adverse events (irAEs) following treatment with ICIs can be severe and sometimes lead to life-threatening situations. Furthermore, the onset of irAEs is unpredictable, as they may develop early after ICI treatment or more than 18 months after treatment initiation.[3] Thus, the early detection of irAEs is sought after in clinical practice.

We herein report a patient who underwent resection had recurred lung cancer and developed irAEs following ICI monotherapy, with serum antibody measurements performed. In this context, we examined the serum antibodies as a tumor-specific response (anti-p53 antibody) and non-specific response (immunoglobulins) and report the humoral immune response to ICI treatment.

CASE REPORT

A 78-year-old woman admitted to our hospital was found to have a right lung tumor. Chest computed tomography (CT) showed a 4.0-cm right upper lobe tumor, and she was diagnosed with right lung cancer (cT3N0M0, stageIIB). A right upper lobectomy and lymph node dissection was performed. Pathological examination revealed the tumor to be pleomorphic carcinoma (pT3N0M0, stageIIB). Although postoperative recovery was favorable, the patient experienced tumor recurrence (lung, pleura, adrenal gland, and bone) 6 months after surgery. Because of the high expression of PD-L1 without other molecular mutations, she received pembrolizumab monotherapy. After five cycles of ICI therapy, the recurrent tumors showed shrinkage (Figure 1a,b). However, a skin rash developed after seven cycles. Although we stopped treatment, pneumonitis occurred 1 month after the development of the skin rash (Figure 1c,d)

During ICI treatment, we conducted monthly measurements of the serum antibody levels, which included both those which were tumor- (anti-p53 antibody) and nonspecific (immunoglobulins). The anti-p53 antibody titer was examined externally (SRL Co., Fukuoka, Japan), while other serum immunoglobulins (IgM, IgG, and IgA) were examined in our hospital. Anti-p53 antibodies and IgM did not increase during ICI treatment (data not shown), but the serum levels of IgG and IgA had gradually increased before

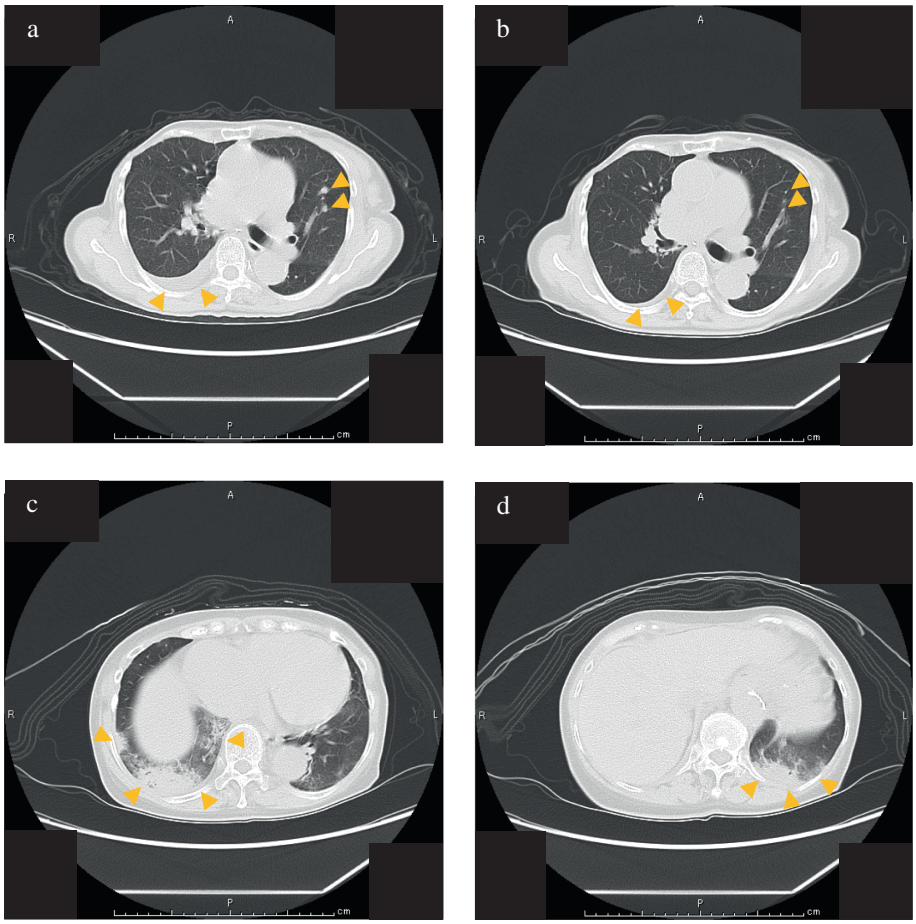

FIGURE 1 Computed tomography (CT) findings pre- (a) and post treatment (b) with immune checkpoint inhibitor (ICI) monotherapy. The left lung nodules and right pleural effusion (arrow) showed regression due to ICI treatment. After seven cycles of ICI treatment, the CT showed pneumonitis (c, d; arrow)

the occurrence of the skin rash (Figure 2). In contrast, the peripheral blood eosinophil count and neutorophil/lymphocyte ratio did not increase through ICI treatment (data not shown).

DISCUSSION

We previously investigated the tumor specific immune response to p53 antigen in a lung cancer patient and detected simultaneous cellular and humoral immune responses.[4,5] Therefore, we examined the humoral immune response as tumor- (anti-p53 antibody) and nonspecific (immunoglobulins) in serum through ICI treatment. The serum levels of IgG and IgA increased before the occurrence of irAEs. These results suggested that B cells can recognize the antigens induced by ICI treatment, and some immunoglobulins might be useful for rapidly detecting an ICI-induced immune response.

It is well known that organ-specific autoantibodies, which mostly consist of IgG, can be present before the onset of clinical symptoms of autoimmune diseases.[6] In ICI treatment, the presence of pre-existing specific autoantibodies has led to the hypothesis that these factors play a role in the modulation of irAE pathogenesis.[7] However, the detection of specific autoantibodies in individual patients with irAEs is very difficult in clinical practice. In our case, IgG antibodies gradually increased during irAEs (Figure 2b). These results suggest that whole antibodies of IgG, rather than specific antibodies, might be useful for detecting irAEs in serum. IgA can neutralize invading pathogens and induce a range of Fc-effector functions to control and clear various bacterial and viral infections.[8] Furthermore, IgA maintains homeostasis of inflammation at mucosal surfaces and in the blood and tissues.[9] It has recently been reported that the diagnosis of celiac disease induced by ICI is based on the measurement of serum IgA antibodies to tissue transglutaminase.[10] In our case, IgA antibodies gradually increased before the occurrence of skin rush (Figure 2a). Similar to the above, these results also suggested that whole antibodies of IgA, not specific ones, might be useful for assessing irAEs. However, we examined serum antibodies in only one case. The further accumulation of clinical experience concerning T cell–B cell interactions in ICI treatment is needed.

Previously, we reported that tumor-infiltrating B cells produced tumor-specific antibodies, such as anti-p53 antibodies, in the tumor microenvironment in cases of lung cancer.[4,5] Therefore, to detect a tumor-specific humoral immune response, we investigated the titers of anti-p53 antibodies in the patient's serum during ICI therapy. The tumor showed

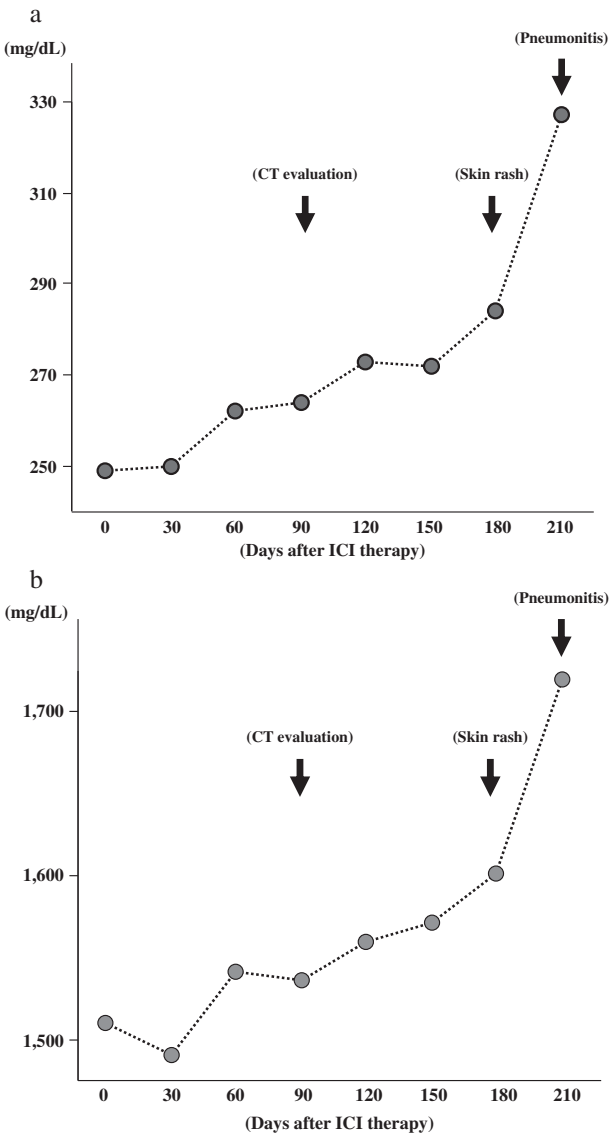

FIGURE 2 The serum levels of IgA (a) and IgG (b) gradually increased during immune checkpoint inhibitor (ICI) treatment. The reference values were IgA (93–393 mg/dl), and IgG (861–1747 mg/dl) in our hospital

shrinkage in response to ICI therapy, but the titers of anti-p53 antibody did not increase (data not shown). Further studies concerning the detection of a tumor-specific humoral immune response in serum through ICI treatment are needed

In conclusion, serum immunoglobulins, such as IgG and IgA, may be useful for the early detection of irAEs in ICI treatment. If serum immunoglobulin levels are increased through ICI therapy, the development of irAEs should be closely monitored. Further controlled studies to confirm these findings are required.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

All authors have no potential conflicts of interest to declare.

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