Letter to the Editor
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A Case of Anti-reticulin Antibody-positivity in Metachronous Double Primary Cancer

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Dear Editor,

Several studies have demonstrated the relationship between autoantibodies and tumors [1]. The anti-reticulin antibody (ARA) was first identified in 1971 and was used as a specific marker for gluten-sensitive enteropathy [2, 3], playing a supportive role in the diagnosis of celiac disease. However, anti-tissue transglutaminase antibody detection has replaced the ARA method as the single test to diagnose celiac disease. To date, ARA has only been identified in patients with autoimmune enteropathy and other types of autoimmune diseases. However, we observed its presence in a patient who was diagnosed as having metachronous double primary cancer. We evaluated the relationship between ARA and malignancy.

A 77-year-old man achieved complete recovery of papillary urothelial carcinoma of the bladder after undergoing transurethral resection of the bladder tumor in October 2003 at Hanyang University Medical Center, Seoul, Korea. In June 2013, he was diagnosed as having adenocarcinoma as a second primary cancer with involvement of multiple lymph nodes and bone metastases. The patient was maintained with hormone therapy and conservative treatment. In October 2014, biochemistry test results showed an alkaline phosphatase level of 176 U/L and AST/ALT levels of 149/166 U/L, both of which were higher than normal levels. The results of viral hepatitis test and complete blood cell count were normal. To differentially diagnose toxic hepatitis, hormone therapy was discontinued. An antinuclear antibody (ANA) test performed to differentially diagnose autoimmune hepatitis was negative. The test tissue was negative for anti-smooth muscle antibody (ASMA) but was positive for R1-ARA (Fig. 1). At that time, the patient had elevated AST/ALT levels due to non-alcoholic fatty liver disease, for which he was solely treated with analgesics.

In this case, the second primary cancer developed nine years and eight months after the primary cancer. Although this is a relatively long period, detection of the autoantibody in a patient with double primary cancer may be of general significance.

ARA is generally detected by indirect immunofluorescence using three types of rat tissues (stomach, kidney, and liver), and its immunofluorescent patterns are classified into five types (R1, R2, R_{KC}, R_{AC}, and Rs) [4]. Among these, R1-ARA is specific to untreated celiac disease [5, 6]. The R1 pattern is immunopositive in the perivascular area of the stomach, kidney, and liver; the area between the gastric glands; the periglomerular and peritubular areas of the kidney; and the areas surrounding the liver parenchyma, sinusoid, and portal vein of the liver.

Natural autoantibodies regulate the immune system. Therefore, it is possible that various types of autoantibodies may be detected in conditions, in which homeostasis is disrupted, in-

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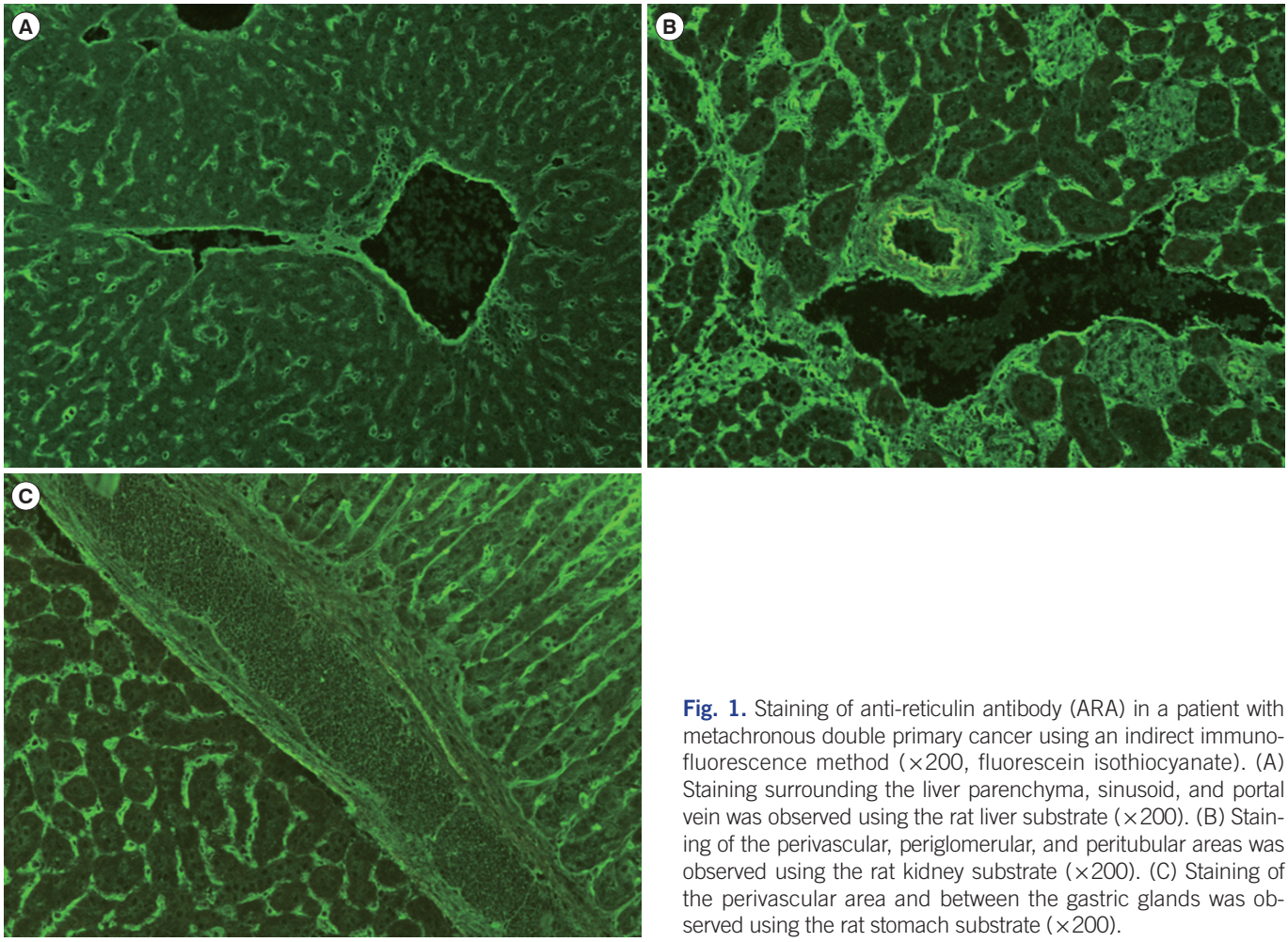

Fig. 1. Staining of anti-reticulin antibody (ARA) in a patient with metachronous double primary cancer using an indirect immunofluorescence method (×200, fluorescein isothiocyanate). (A) Staining surrounding the liver parenchyma, sinusoid, and portal vein was observed using the rat liver substrate (×200). (B) Staining of the perivascular, periglomerular, and peritubular areas was observed using the rat kidney substrate (×200). (C) Staining of the perivascular area and between the gastric glands was observed using the rat stomach substrate (×200).

cluding malignant tumors [1]. In addition, autoantibodies have been transiently detected in patients undergoing treatments such as interleukin therapy for malignant tumors [7, 8]. However, to our knowledge, there has been no previously reported case of a patient with autoantibody-positive metachronous double primary cancer.

In the current case, R1-ARA was confirmed in a patient with metachronous double primary cancer without a history of bowel disease. This suggests that other mechanisms may be involved in the synthesis of R1-ARA. The current patient did not receive interleukin treatment. However, it is probable that this patient had transient autoantibodies that were only observed during cancer treatment. Alternatively, it is possible that the metachronous double primary cancer occurred as a result of cancer evolution due to genetic defects in the host's immune system. We also consider the possibility that the autoantibodies may have arisen from a systemic inflammatory response.

Further studies are warranted to clarify the relationship between the immunofluorescent patterns of ARA and malignant diseases, which will provide more information on the relevant mechanisms. Extensive investigations based on Korean and overseas ARA-positive cases may be helpful for diagnosing and treating patients.

Authors' disclosure of potential conflict of interest

No potential conflicts of interest relevant to this article were reported.

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