CASE REPORT

A Case of Henoch-Schönlein Purpura Complicated by Hepatocellular Carcinoma

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Abstract:
Although Henoch-Schönlein purpura (HSP) is known to be accompanied by malignancies, cases with hepatobiliary cancer are extremely rare. A 62-year-old man with palpable purpura rapidly extending to both lower legs was admitted to our hospital. He was undergoing follow-up for cirrhosis caused by chronic hepatitis B virus infection and hepatocellular carcinoma (HCC). He had renal dysfunction with hematuria and proteinuria and abdominal pain. Based on the clinical presentation and skin biopsy findings, he was diagnosed with HSP. The administration of steroids resulted in the rapid improvement of the patient’s symptoms and he was discharged 12 days after admission.

Key words: Henoch-Schönlein purpura, Hepatocellular carcinoma, Steroid therapy

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Introduction

Henoch-Schönlein purpura (HSP) is systemic small-vessel vasculitis that involves various organs, including the skin, gastrointestinal tract, kidneys, and joints. Because HSP is pathologically characterized by the tissue deposition of immune complexes containing immunoglobulin A (IgA), it is also called IgA vasculitis (1). HSP develops more frequently in children than adults, with clinical symptoms such as non-thrombocytopenic palpable purpura, abdominal pain, arthralgia, and edema (2). More than 80% of patients recover spontaneously with only supportive care. Previous studies have indicated that HSP might be triggered by infection, food reactions, exposure to cold, insect bites, and drug allergies (3). However, the precise mechanisms underlying the development of HSP remain to be elucidated. It has also been reported that malignancies can cause the development of HSP in adults (4). Although abnormal immune responses play a central role in the development of HSP, the pathological mechanism of HSP accompanied by malignancy is poorly understood.

We describe an unusual case of HSP complicated by hepatocellular carcinoma (HCC) in a patient who was successfully treated with steroid therapy.

Case Report

A 62-year-old man with palpable purpura on both lower legs was admitted to our hospital. Ten days prior to his admission, the purpura first appeared on the right lower extremity and rapidly extended to both legs. Over the past 6 years, he had been followed up for cirrhosis caused by chronic hepatitis B virus infection and HCC. He had renal dysfunction with hematuria and proteinuria and abdominal pain. Based on the clinical presentation and skin biopsy findings, he was diagnosed with HSP. The administration of steroids resulted in the rapid improvement of the patient’s symptoms and he was discharged 12 days after admission.

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On physical examination, the patient was afebrile. Palpable purpura was observed on the entire lower extremities but not on the face, trunk, or upper extremities (Fig. 2). Neither edema nor arthralgia was observed. A laboratory examination revealed mild elevation of serum aspartate aminotransferase (AST, 60 IU/L) and γ-glutamyltransferase (γ-GTP, 120 IU/L), and an abnormal increase in blood urea nitrogen (BUN, 31 mg/dL) and serum creatinine (2.81 mg/dL) (Table). A blood analysis showed a remarkable increase in the white blood cell count (19,000/μl) and the patient’s C-reactive protein (CRP, 14.7 mg/dL) level was extremely elevated. Although the patient was hepatitis B surface antigen-positive, HBV-DNA was not detected in response to entecavir. The serum levels of IgG (3,114 mg/dL) and IgA (808 mg/dL) were also markedly increased. The complement values were within the normal limit for C3 and C4. A urinalysis revealed hematuria and proteinuria. The patient’s α-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) levels were slightly increased to 9.7 ng/mL and 165 mAU/mL, respectively. The patient’s Child-Pugh score was 9 (class B).

Unexpectedly, acute abdominal pain developed on the day after admission. Plain CT revealed proximal jejunal wall thickening, indicating the involvement of the gastrointestinal tract (Fig. 3). It has been reported that HSP frequently shows a wide range of endoscopic findings, including redness, swelling, petechiae, submucosal hemorrhage, purpura, erosion, and ulceration of the mucosa in the gastrointestinal tract, particularly in the jejunum (5). Although an endoscopic examination was important for distinguishing the patient’s condition from other digestive tract diseases, such as Crohn’s disease, we failed to obtain informed consent to perform gastrointestinal endoscopy. Oral intake was avoided to promote bowel rest. A skin biopsy was subsequently performed by a dermatologist (Fig. 4). Hematoxylin and eosin (H&E) staining of the biopsy specimen showed leukocytoclasis and direct immunofluorescence showed IgA deposition on the blood vessel walls of the dermal papillary layer. Based on these findings, the patient was diagnosed as having HSP. Steroid therapy with prednisolone (40 mg/day, intravenous) was initiated to treat the patient’s renal dysfunction and abdominal pain.

The clinical course after the initiation of steroid treatment was uneventful (Fig. 5). The patient’s purpura, abdominal pain, and renal dysfunction improved rapidly. Oral
Table. Laboratory Data.

<table>
<thead>
<tr>
<th>Blood cell count</th>
<th>Blood chemistry</th>
<th>Serology</th>
<th>Tumor markers</th>
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<tbody>
<tr>
<td>WBC 19,000/μL</td>
<td>TP 6.2 g/dL</td>
<td>CRP 14.7 mg/dL</td>
<td>AFP 9.7 ng/mL</td>
</tr>
<tr>
<td>RBC 3.57×10⁵/μL</td>
<td>Alb 2.2 g/dL</td>
<td>IgG 3.114 mg/dL</td>
<td>AFP-L3 55.9%</td>
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<td>Hb 10.5 g/dL</td>
<td>T-Bil 1.1 mg/dL</td>
<td>IgA 808 mg/dL</td>
<td>PIVKA-II 165 mAU/mL</td>
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<tr>
<td>Ht 31.1%</td>
<td>AST 66 IU/L</td>
<td>IgM 49 mg/dL</td>
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</tr>
<tr>
<td>Pt 22.9×10⁵/μL</td>
<td>ALT 20 IU/L</td>
<td>C3 90 mg/dL</td>
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<tr>
<td></td>
<td>LDH 241 IU/L</td>
<td>C4 21 mg/dL</td>
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<td>Coagulation</td>
<td>ALP 383 IU/L</td>
<td>HBsAg (+)</td>
<td>Blood +2</td>
</tr>
<tr>
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<td>γ-GTP 146 IU/L</td>
<td>HBcAb (+)</td>
<td>Glucose +3</td>
</tr>
<tr>
<td>PT-INR 1.40</td>
<td>BUN 31 mg/dL</td>
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<td>PT 48%</td>
<td>Cre 2.81 mg/dL</td>
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<td>APTT 44.4 sec</td>
<td>NH₃ 22 μg/dL</td>
<td>HCV-Ab (−)</td>
<td></td>
</tr>
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</table>

Figure 3. The findings of computed tomography (CT) at the onset of abdominal pain. Plain CT images revealed proximal jejunal wall thickening (arrows).

intake was restarted on day 5 after admission. On day 9, the levels of BUN and creatinine were 18 mg/dL and 0.74 mg/dL, respectively. Although the patient’s proteinuria improved, his hematuria continued. The CRP level fell to 4.0 mg/dL. He was discharged 12 days after admission on oral prednisolone. The dosage of prednisolone was reduced by 5 mg/day for 2 weeks in the outpatient clinic. When the dosage was reduced to 30 mg/day, purpura reappeared on both legs. The administration of prednisolone (30 mg/day) was continued; however, the patient died of HCC progression approximately two months after the diagnosis of HSP.

Discussion

Solid tumors occur more frequently than hematological malignancies as causative malignant tumors associated with HSP (6). Cases involving lung cancer and prostate cancer have often been reported; in contrast, there are very few reports on cases involving hepatobiliary tumors (7). The relevant hematological malignancies mostly include multiple myeloma and malignant lymphoma; leukemia is extremely rare (8). Although the mechanisms by which malignancy contributes to the development of HSP remain obscure, tumor-derived neoantigens reportedly lead to abnormal immunological reactions against small blood vessels (9). Other mechanisms, such as decreased immunocomplex clearance, antibody switching from IgM to IgA by dysregulated lymphocytes, and the excessive release of inflammatory cytokines by tumor cells, might play important roles in the development of HSP (8). Previous reports have shown that the development of HSP is observed not only in patients with early-stage malignancies but also in those with advanced-stage malignancies (7-9). In our case, history taking and a physical examination failed to identify possible causes of HSP, which include infection, food reactions, and drug allergies. It is difficult to clarify a direct causal relationship between HCC and HSP. However, the re-emergence of purpura was observed when the prednisolone dosage was reduced (30 mg/day). It is possible that the reduction in the dose of prednisolone without treatment for HCC caused an exacerbation of HSP. Together, these findings indicate the possibility that HSP was associated with HCC.

The diagnostic criteria for HSP defined by the American College of Rheumatology (ACR) requires the presence of two out of four of the following features: palpable purpura without thrombocytopenia, age at onset <20 years, bowel angina, and histological findings of leukocytoclastic vasculitis (10). Although the diagnostic sensitivity and specificity based on these criteria are reported to be 87.1% and 87.7%, respectively, there are cases in which it is difficult to make a diagnosis (e.g., when the onset of cutaneous purpura is delayed in adult patients). The diagnostic criteria proposed by the European League Against Rheumatism (EULAR) and the Paediatric Rheumatology European Society (PReS) states that for a diagnosis of HSP, palpable purpura should be accompanied by at least two of the following four conditions: extensive abdominal pain, IgA deposition on a biopsy specimen, arthritis or arthralgia, and renal involvement (hematuria and/or proteinuria) (11). These diagnostic criteria are characterized by indicators that include joint and renal symptoms, but not age. Because the present case had not only palpable purpura but also abdominal pain and renal dysfunction with hematuria and proteinuria, the diagnosis of
Figure 4. The pathological examination of skin biopsy samples. (A) Hematoxylin and Eosin staining showed leukocytoclastic vasculitis (arrows) with epidermal microabscess formation (arrowheads) (x200). (B) Direct immunofluorescence using anti-IgA antibody revealed IgA deposition (arrows) in the blood vessel walls of the dermal papillary layer (x200).

HSP was consistent with both sets of diagnostic criteria. In addition, the skin biopsy specimens of the present case revealed both neutrophilic infiltration into the small dermal blood vessels and IgA deposition within the vessel walls. Although the definitions for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference documented that HSP is a small vessel vasculitis with IgA-dominant immune deposits (12), some patients have no evidence of IgA deposition. While the serum levels of IgA are elevated in such patients as in the present case-some studies have reported that approximately 50% of patients do not show abnormal levels (13).

In HSP patients, renal involvement is found in 30-40% of children and 45-85% of adults (14). Moreover, the incidence of progression to end-stage renal failure is <5% in children and as high as 30% in adults, who have a poor prognosis (15). A double-blind randomized controlled trial in which 171 HSP patients of ≤16 years of age were enrolled reported that the administration of steroid had the potential to not only improve renal dysfunction but also relieve abdominal pain and arthralgia (16). Steroid therapy is therefore considered to be indicated in patients with these symptoms (17, 18); however, steroids reportedly have no preventive effects against the onset of gastrointestinal tract and renal involvement (19). Furthermore, there have been reports indicating the effectiveness of the concomitant administration of a steroid with another immunosuppressive drug or switching from a steroid to an immunosuppressive drug (20, 21). In the present case, in which the patient had renal failure and episodes of abdominal pain, the administration of a steroid from day 2 promptly improved the patient’s symptoms. On discharge, the patient had normal BUN and creatinine levels.

Reduced renal blood flow is frequently observed in cir-
rhocytic patients and is known to contribute to the impairment of the renal function (22). This trend in patients with decompensated cirrhosis is remarkable in comparison to those with compensated cirrhosis. Although the patient showed normal serum creatinine levels before the development of HSP, his case was complicated by decompensated cirrhosis (Child-Pugh score: 9). Given that the creatinine level remains within the normal range unless the renal function is disturbed by <50%, it is highly possible that he had renal dysfunction. Fortunately, the patient’s creatinine level returned to normal following the initiation of steroid therapy; however, special attention is required in the treatment of cirrhotic patients with HSP in view of their renal function.

It the present case, the dosage of prednisolone was reduced by 5 mg/day for 2 weeks in the outpatient clinic. When the dosage was reduced to 30 mg/day, purpura reappeared on both legs. It is possible that the discontinuation (or dose reduction) of prednisolone without anticancer treatment results in the exacerbation of HSP in patients with malignancies. Further studies are needed to investigate the appropriate dose of steroids and to determine an efficient strategy for reducing the dose of steroids.

In conclusion, we reported a case of HSP complicated by HCC that was successfully treated with steroids. Since many uncertainties remain concerning the pathology of HSP accompanied by malignancy, further studies and analyses of larger sample sizes are required in order to clarify the pathology and explore different therapeutic approaches.

The authors state that they have no Conflict of Interest (COI).

References


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