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**Hemophagocytic syndrome as a complication of acute pancreatitis: A case report**

Han CQ *et al*. HPS as a complication of AP

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**Abstract**

BACKGROUND

Haemophagocytic syndrome (HPS) is rarely seen in patients with acute pancreatitis (AP). HPS as a complication of AP in patients without any previous history has not been elucidated.

CASE SUMMARY

A 46-year-old man was admitted for symptom of persistent abdominal pain, nausea, and vomiting for 2 d after heavy drinking. During hospital stay, he suddenly developed skin rash and a secondary fever. The laboratory findings revealed progressive pancytopenia, abnormal hepatic tests, and elevation of serum triglyceride, ferritin, and lactate dehydrogenase levels. However, apparent bacterial or viral infections were not detected. He was also possibly related to autoimmune diseases because of positive expression of various autoimmune antibodies and no remarkable past history. Finally, the bone marrow examination showed a histiocytic reactive growth and prominent hemophagocytosis, which resulted in a diagnosis of HPS. Unexpectedly, the patient responded well to the immunosuppressive therapy.

CONCLUSION

HPS is a very rare extrapancreatic manifestation of AP. The diagnosis relies on bone marrow examination and immunosuppressive therapy is effective. For AP with skin changes, the possibility of HPS should be considered during clinical work.

**Key words:** Haemophagocytic syndrome; Acute pancreatitis; Immunosuppressive therapy

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**Core tip:** Haemophagocytic syndrome is a rare extrapancreatic manifestation of acute pancreatitis. We herein report the first such case to share our experience with its diagnosis and treatment. The patient responded well to the immunosuppressive therapy. Early diagnosis and treatment are crucial.

**INTRODUCTION**

Haemophagocytic syndrome (HPS) is an uncommon disorder that may be characterized by fever, peripheral blood pancytopenia, liver dysfunction, coagulation abnormalities, and hepatosplenomegaly[[1](#_ENREF_1), [2](#_ENREF_2)]. It may be triggered by genetic disorders, malignant neoplasms, viral infections, and autoimmune disorders[[3-5](#_ENREF_3)]. Acute pancreatitis (AP) and HPS are sporadically observed in the course of systemic lupus erythematosus (SLE) or fulminant ulcerative colitis secondary to autoimmune diseases[[2](#_ENREF_2), [6](#_ENREF_6), [7](#_ENREF_7)]. We herein report such a case to share our experience with its diagnosis and treatment.

**CASE PRESENTATION**

***Chief complaints***

A 46-year-old man was admitted for symptom of persistent abdominal pain, nausea, and vomiting for 2 d after heavy drinking and then transferred to our hospital.

***History of present illness***

The patient’s symptoms started with mild abdominal pain, which had worsened in the last 2 h.

***History of past illness***

He had no previous history except for smoking.

***Physical examination***

The physical examination on admission revealed a discontinuous fever (38 ℃) (Figure 1B) and upper abdomen tenderness. His skin was normal.

***Laboratory examinations***

The laboratory data showed significantly increased serum levels of amylase (1454.9 U/L), lipase (1705.28 U/L), white blood cell count (17 G/L), positive C-reactive protein (4.8 mg/mL), and erythrocyte sedimentation rate (58 mm/h) (Figure 1D-F), slightly elevated glucose (7.71 mmol/L) and D-dimer (1.63 mg/L), slightly reduced calcium (1.88 mmol/L), and hypoalbuminemia (31.0 g/L). The coagulation, hepatic, and renal functions were all within normal limits. The detailed laboratory values are described in Table 1.

***Imaging examinations***

Pancreatic enlargement and peripancreatic seepage on computerized tomography confirmed the diagnosis of AP (Figure 2). Then, the patient was given enteral nutrition *via* a jejunal nutrition tube (Figure 1C) and treated with pantoprazole sodium (40 mg per 8 h), octreotide aetate (0.6 mg/q12h), and anti-inflammatory drugs (ornidazole 0.5 g/q8h, meropenem 0.5 g/q8h, *etc.*). Traditional Chinese medicine catharsis was performed for the prevention of intestinal function failure (Figure 1A). The symptoms of the patient gradually disappeared. He had no febrile and each index was close to the baseline level (Figure 1D-F). Bilateral pleural effusion was absorbed better than before (Figure 3). Surprisingly, from the hospital days 11 to 17, the patient suddenly developed a secondary fever and the highest temperature reached 39.7 ℃ (Figure 1B). We strengthened the antibiotic treatment, including antifungal therapy, although blood culture did not find any evidence of bacterial or fungal infection. Unfortunately, although the temperature was controlled, his general condition deteriorated. On day 16 after hospitalization, he developed a rash on the trunk, upper limbs, and cruses (Figure 4F), then the indexes of autoimmune disease (e.g., SLE), such as anti-ANA (1:1000), anti-SSA (+), Ro-52-Ab (+), IgG (15.80 g/L), and IgE (471.1 IU/mL), were evaluated. Additionally, he also developed pancytopenia (3.18 g/L of white blood cells, 109 g/L of hemoglobin, and 88 g/L of platelets), hepatic dysfunction (alanine aminotransferase [ALT], 390 U/L; aspartate amino transferase [AST], 172 U/L), and a marked elevation of triglyceride (3.51 mmol/L), ferritin (5850 μg/L), and serum lactic acid dehydrogenase (LDH, 396 U/L) (Figure 4A-E), but his coagulation function was normal without significant abdominal ultrasonography findings.

**FINAL DIAGNOSIS**

Based on the above findings, a diagnosis of HPS was highly suspected and a peripheral blood smear and bone marrow examination were planned due to the complicated symptoms. Hemophagocytic cells were found in peripheral blood smears (Figure 4G) and the bone marrow examination showed a histiocytic reactive growth and prominent hemophagocytosis (Figure 4H). Thus, HPS as a complication of AP was finally diagnosed.

**TREATMENT**

The patient was then treated with liver-protecting drugs, antiallergic drugs, and hexadecadrol 5 mg/d for 4 consecutive days. By day 20, his symptoms of pancytopenia, liver function, and LDH and ferritin elevations were improved. On the day that the patient left the hospital (day 26), the laboratory parameters were largely close to the baseline levels again.

**OUTCOME AND FOLLOW-UP**

At the 1-mo follow-up visit after discharge, the patient did not take any drugs and had no symptoms or signs without any recurrence.

**DISCUSSION**

Other abnormal clinical and laboratory findings consistent with the diagnosis of HPS include cerebromeningeal symptoms, jaundice, edema, lymph node enlargement, skin rash, hepatic enzyme abnormalities, hypoproteinemia, and hyponatremia[[8](#_ENREF_8)]. In the present case, the symptoms of patient gradually recovered after effective treatment. However, the results of laboratory re-examination were incomprehensibly deteriorative. He developed a secondary fever, rash, pancytopenia, hepatic dysfunction, hyperferritinemia, and elevation of serum triglyceride and LDH levels. The bone marrow examination proved that he had concurrent HPS[[9](#_ENREF_9)].

He had no remarkable past medical history, therefore we first considered if HPS was bacteria or virus-associated or malignancy-associated. However, no active infections with viruses as coxsackievirus, enterovirus, cytomegalovirus, hepatitis B virus, Epstein-Barr virus and other respiratory tract infective viruses were observed. Neither prominent hemophagocytosis nor hematological malignancies were detected. There were also no abnormal findings on abdominal CT and tumor markers analysis except slightly elevated CA125. We also suspected concurrent autoimmune diseases because HPS was reported more commonly in patients with pre-existing SLE. However, besides some autoimmune antibodies showing positive expression, no evidence suggested an underlying autoimmune disease.

There was another possibility that HPS was the side effect of pharmaceutical treatment. We indeed used some drugs that could cause rash, pancytopenia, and hepatorenal dysfunction, *e.g.*, antibiotics such as cefoperazone sodium, fluconazole, or teicoplanin and other acid suppression drugs such as pantoprazole sodium. However, all of these are generally well tolerated and therapeutic measures were appropriate[[10-13](#_ENREF_10)]. Additionally, some common adverse reactions of these drugs, such as headache, nausea, vomiting, diarrhea, and pruritus did not occur[[14-17](#_ENREF_14)]. Therefore, the possibility that it was the side effect of pharmaceutical treatment was ruled out.

HPS is a rare extrapancreatic manifestation of AP. A ambiguous association between AP and HPS was first mentioned in 1998 by Kanaji *et al*[[2](#_ENREF_2)], who found HPS associated with fulminant ulcerative colitis and concurrent AP. So far, there have been just two reports about HPS associated with AP in patients with SLE disease.

**CONCLUSION**

We have described the first case of HPS as a complication of AP, which was successfully treated with immunosuppressive therapy. HPS is a severe condition which requires both early diagnosis and treatment, and HPS as one of the extrapancreatic manifestations of AP should be considered in the future.

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**REFERENCES**

1 **Reiner AP**, Spivak JL. Hematophagic histiocytosis. A report of 23 new patients and a review of the literature. *Medicine (Baltimore)* 1988; **67**: 369-388 [PMID: 3054418 DOI: 10.1097/00005792-198811000-00002]

2 **Kanaji S**, Okuma K, Tokumitsu Y, Yoshizawa S, Nakamura M, Niho Y. Hemophagocytic syndrome associated with fulminant ulcerative colitis and presumed acute pancreatitis. *Am J Gastroenterol* 1998; **93**: 1956-1959 [PMID: 9772064 DOI: 10.1111/j.1572-0241.1998.00554.x]

3 **Ishii E**, Ohga S, Imashuku S, Kimura N, Ueda I, Morimoto A, Yamamoto K, Yasukawa M. Review of hemophagocytic lymphohistiocytosis (HLH) in children with focus on Japanese experiences. *Crit Rev Oncol Hematol* 2005; **53**: 209-223 [PMID: 15718147 DOI: 10.1016/j.critrevonc.2004.11.002]

4 **Haque WM**, Shuvo ME, Rahim MA, Mitra P, Samad T, Haque JA. Haemophagocytic syndrome in an adult suffering from pyrexia of unknown origin: an uncommon presentation of tuberculosis: a case report. *BMC Res Notes* 2017; **10**: 110 [PMID: 28241857 DOI: 10.1186/s13104-017-2434-y]

5 **Janka GE**, Lehmberg K. Hemophagocytic syndromes--an update. *Blood Rev* 2014; **28**: 135-142 [PMID: 24792320 DOI: 10.1016/j.blre.2014.03.002]

6 **Abdallah M**, B'Chir Hamzaoui S, Bouslama K, Mestiri H, Harmel A, Ennafaa M, M'Rad S, Ben Dridi M. [Acute pancreatitis associated with hemophagocytic syndrome in systemic lupus erythematous: a case report]. *Gastroenterol Clin Biol* 2005; **29**: 1054-1056 [PMID: 16435516 DOI: 10.1016/s0399-8320(05)88191-6]

7 **Elqatni M**, Mekouar F, Sekkach Y, Elomri N, Fatihi J, Amezyane T, Abouzahir A, Ghafir D. [Haemophagocytic syndrome as a complication of acute pancreatitis during systemic lupus erythematosus]. *Ann Dermatol Venereol* 2012; **139**: 46-49 [PMID: 22225742 DOI: 10.1016/j.annder.2011.10.398]

8 **Henter JI**, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; **48**: 124-131 [PMID: 16937360 DOI: 10.1002/pbc.21039]

9 **Oh HS**, Kim M, Lee JO, Kim H, Kim ES, Park KU, Kim HB, Song KH. Hemophagocytic lymphohistiocytosis associated with SFTS virus infection: A case report with literature review. *Medicine (Baltimore)* 2016; **95**: e4476 [PMID: 27495089 DOI: 10.1097/MD.0000000000004476]

10 **Baltatzis M**, Jegatheeswaran S, O'Reilly DA, Siriwardena AK. Antibiotic use in acute pancreatitis: Global overview of compliance with international guidelines. *Pancreatology* 2016; **16**: 189-193 [PMID: 26804006 DOI: 10.1016/j.pan.2015.12.179]

11 **Mourad MM**, Evans R, Kalidindi V, Navaratnam R, Dvorkin L, Bramhall SR. Prophylactic antibiotics in acute pancreatitis: endless debate. *Ann R Coll Surg Engl* 2017; **99**: 107-112 [PMID: 27917667 DOI: 10.1308/rcsann.2016.0355]

12 **Rada G**, Peña J. Is antibiotic prophylaxis beneficial in acute pancreatitis?--First update. *Medwave* 2015; **15**: e6125 [PMID: 25938428 DOI: 10.5867/medwave.2015.03.6125]

13 **Choi HM**, Choi MH, Yang YW. A Case of Teicoplanin-Induced Pancytopenia Caused by Excessive Dosing. *Am J Ther* 2016; **23**: e307-e310 [PMID: 24263159 DOI: 10.1097/MJT.0000000000000008]

14 **Ren X**, Liu D, Ding N, Huang K, Xiong Y, Du G, Zeng F. Safety evaluation of cephalosporins based on utilization and adverse drug events: analysis of two databases in China. *Expert Opin Drug Saf* 2012; **11**: 689-697 [PMID: 22708900 DOI: 10.1517/14740338.2012.699037]

15 **Xie JX**, Wei JF, Meng L. Teicoplanin-induced hepatocellular liver injury: a case report and literature review of 17 cases in mainland China. *Int J Clin Pharmacol Ther* 2014; **52**: 525-529 [PMID: 24691063 DOI: 10.5414/CP202060]

16 **Holloway WJ**, Palmer D. Clinical applications of a new parenteral antibiotic in the treatment of severe bacterial infections. *Am J Med* 1996; **100**: 52S-59S [PMID: 8678098 DOI: 10.1016/s0002-9343(96)00108-8]

17 **Schiller D**, Maieron A, Schöfl R, Donnerer J. Drug fever due to a single dose of pantoprazole. *Pharmacology* 2014; **94**: 78-79 [PMID: 25228460 DOI: 10.1159/000364781]

**Footnotes**

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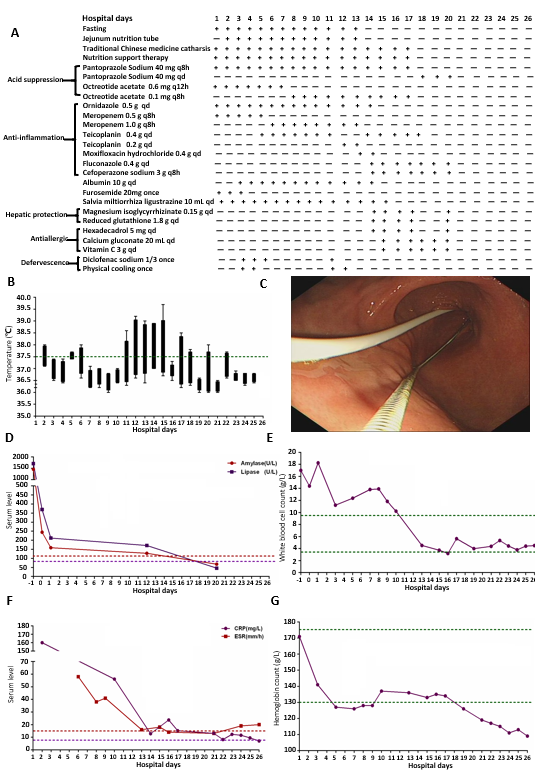
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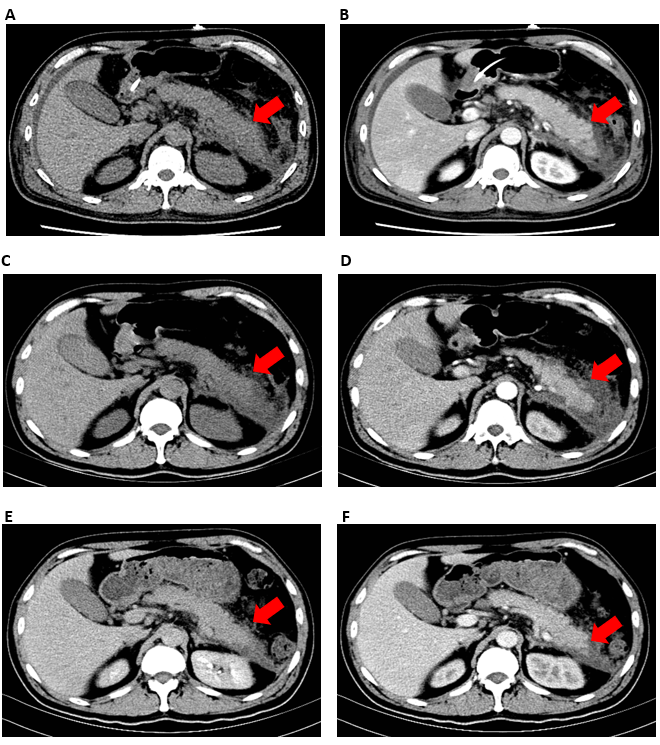
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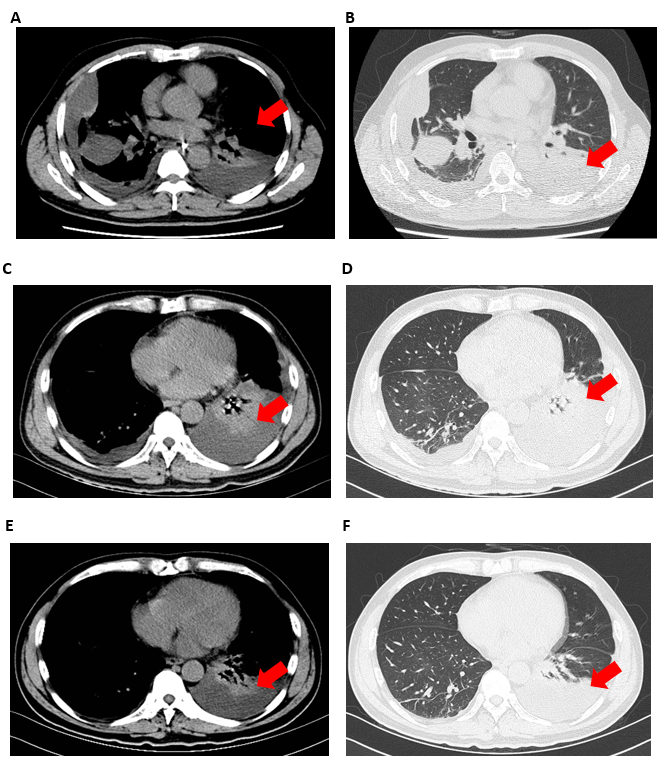
**Figure Legends**



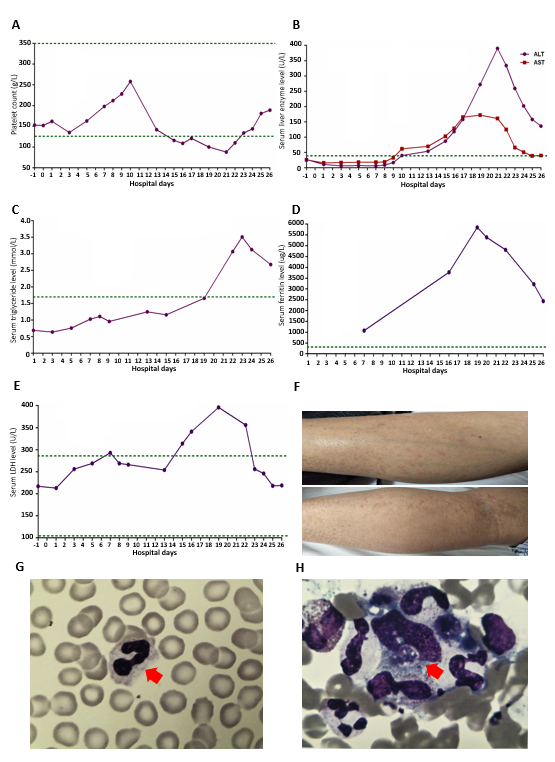
**Figure 1 Results of examinations.** A: Detailed therapeutic measures taken for the patient with acute pancreatitis during the time of hospitalization. Nutrition support therapy included 5% glucose, compound sodium chloride, hetastarch, mix sugar electrolyte, fructose, compound amino acid peptide, glutamine dipeptide, multi-vitamin, and fish oil fat emulsion; B: Temperature change curve of the patient. The measuring frequency was four times a day; C: Jejunum nutrition tube was placed by gastroscopy; D-G: Changes of amylase, lipase, white blood cell count, C-reactive protein, erythrocyte sedimentation rate, and hemoglobin during hospitalization.



**Figure 2 Images of abdominal computed tomography.** A and B: Contrast-enhanced computed tomography imaging of the pancreas showed pancreatic swelling, peripancreatic infiltration, and bilateral fascia thickening on the fourth day of hospitalization; C and D: The pancreatic swelling and peripancreatic fluid collections were meliorated on day 13; E and F: The peripancreatic seepage almost recovered on day 23.



**Figure 3** **Images of thoracic computed tomography.** A and B: On the fourth day, thoracic computed tomography showed bilateral pleural effusion with partially encapsulated effusion. The lungs also showed scattered linear and lamellar high-density shadows, which were considered to be due to an infectious disease; C and D: Thoracic computed tomography indicated that encapsulated effusion was gradually absorbed but the left lung showed segmental atelectasis on day 13; E and F: Bilateral pleural effusion completely disappeared and segmental atelectasis was recovered on day 23.



**Figure 4 Changes of indexes after** **effective treatment.** A-E: Changes of platelets and serum levels of alanine aminotransferase, aspartate amino transferase, triglyceride, ferritin, and lactic acid dehydrogenase during hospitalization; F: The patient suddenly developed skin rash; G: No obvious abnormality was found in the peripheral blood smear (original magnification, 1 × 103); H: Overactive macrophage phagocytosis, erythrocytes, leucocytes, platelets, and their precursors were also not found in the bone marrow aspiration specimen (original magnification, 1 × 103). ALT: Alanine aminotransferase; AST: Aspartate amino transferase.

**Table 1 Laboratory findings for the patient with acute pancreatitis during hospitalization**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Day** | **Index** | **Value** | **Range** | **P/N** |
| 1 | Calcium | 1.88 | 2.03-2.54 mmol/L |  |
| 1 | Glucose | 7.71 | 3.9-6.1 mmol/L |  |
| 1 | Albumin | 31.0 | 35-55 g/L |  |
| 1 | Creatinine | 86.6 | 44.0-133.0 μmol/L |  |
| 1 | D-Dimer | 1.63 | < 0.5 mg/L |  |
| 6 | PCT | 0.28 | < 0.5 ng/mL |  |
| 7 | CA125 | 320.0 | < 35.0 U/mL |  |
| 7 | CA153 | 8.2 | < 31.3 U/mL |  |
| 7 | CA199 | 6.5 | < 37.0 U/mL |  |
| 14 | Anti-ANA | 1:1000 | < 1:100 |  |
| 14 | IgG | 15.80 | 7.51-15.60 g/L |  |
| 14 | IgA | 2.93 | 0.82-4.53 g/L |  |
| 14 | IgM | 0.634 | 0.46-3.04 g/L |  |
| 15 | Anti-TPO | 384.63 | < 5.61 IU/mL |  |
| 15 | Anti-TG | 427.53 | < 4.11 IU/mL |  |
| 15 | FT3 | 2.0 | 2.63-5.7 pmol/L |  |
| 16 | C3 | 0.395 | 0.79-1.52 g/L |  |
| 16 | C4 | 0.052 | 0.16-0.38 g/L |  |
| 16 | ASO | 49.7 | < 200.0 IU/mL |  |
| 16 | IgG4 | 0.892 | 0.03-2.01 g/L |  |
| 19 | IgE | 471.17 | 1-190 IU/mL |  |
| 8 | T-SPOT.TB |  |  | + |
| 14 | Anti-nRNP |  |  | - |
| 14 | Anti-SSA |  |  | + |
| 14 | Anti-SSB |  |  | - |
| 14 | ADA |  |  | - |
| 14 | DE |  |  | - |
| 14 | RA-54 |  |  | - |
| 14 | ACA |  |  | - |
| 14 | AHA |  |  | - |
| 14 | Ro-52-Ab |  |  | + |
| 15 | CoxB3-IgM |  |  | - |
| 15 | CoxB5-IgM |  |  | - |
| 15 | Evs-RNA |  |  | - |
| 15 | CMV-IgM |  |  | - |
| 15 | pANCA |  |  | - |
| 15 | cANCA |  |  | - |
| 15 | GBM-Ab |  |  | - |
| 15 | EB-DNA |  |  | - |
| 17 | HBV |  |  | - |
| 17 | HCV |  |  | - |
| 17 | HIV |  |  | - |
| 20 | Type A influenza virus |  |  | - |
| 20 | Type B influenza virus |  |  | - |
| 20 | Respiratory syncytial virus |  |  | - |
| 20 | Adenovirus |  |  | - |
| 20 | Type 1 parainfluenza virus |  |  | - |
| 20 | Type 2 parainfluenza virus |  |  | - |
| 20 | Type 3 parainfluenza virus |  |  | - |

P/N: Positive/negative; PCT: Procalcitonin; Anti-ANA : Anti-nuclear antibody; Anti-TPO: Anti-thyroid peroxidase antibody; Anti-TG: Anti-thyroglobulin antibody; FT3: Free triiodothyronine; C3: Complement 3; ASO: Antistreptolysin; T-SPOT.TB: Tuberculosis T cell spot test; Anti-nRNP: Anti-nuclear ribonucleoprotein; Anti-SSA: Anti-Sj gren syndrome A antibody; Anti-SSB: Anti-Sj gren syndrome B antibody; ADA: Anti-dsDNA antibody; DE: Anti-ribosomal P protein antibody; RA-54: Anti-nucleosome antibody; ACA: Anti-cardiolipin antibody; AHA: Anti-histone antibody; Ro-52-Ab: Ro-52 antibody; Cox: Coxsackievirus; Evs: Enterovirus; CMV: Cytomegalovirus; pANCA: Anti-antineutrophilic perinuclear antibody; cANCA: Anti-antineutrophilic cytoplasmic antibody; GBM-Ab: Glomerular basement membrane antibody; EB: Epstein-Barr virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.