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Clinical observation of immunity in patients with secondary infection from severe acute pancreatitis

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Abstract
Objectives To observe immune system changes in patients with secondary infection from severe acute pancreatitis (SAP).
Methods Seventy-nine patients were recruited. The percentages of CD4+, CD8+, natural killer (NK), HLA-DR+ cells and B lymphocytes, and the CD4+/CD8+ ratio, were determined. In addition, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), and interleukin-4 (IL-4) serum levels were determined on days 1, 7, 14, and 28.
Results Fifteen patients had a secondary infection. The immune response of the infected group was quite different from the non-infected group, with a higher percentage of CD4+ and HLA-DR+ cells on days 1, 7, 14 and 28, a higher percentage of CD8+ and NK cells on days 14 and 28, a reduced CD4+/CD8+ ratio, and a reduction in B lymphocytes. The cytokine levels in the infected group were different from the non-infected group, with a rise in TNF-α and IL-6 through the first 2 weeks, but dropping at 1 month. IL-10 and IL-4 increased initially, but then dropped over the next 3 weeks.
Conclusions An early excessive immune response followed by a subsequent immune deficiency is closely related to secondary SAP infection.

Keywords Severe acute pancreatitis · Immunity · Secondary infection

Introduction

Severe acute pancreatitis (SAP) is a common emergency in abdominal surgery and has a substantial mortality risk of 10–30 % [1, 2]. The factors responsible for high patient mortality in SAP are immune dysfunction in the early stages (within the first week), and secondary infection with pancreatic necrosis in the later stages (usually after 10 days) [3–5]. The patient's life is at risk due to local and systemic complications, which lead to multiple organ dysfunction syndrome (MODS) [6].

Clinical and experimental studies support the theory of excessive systemic inflammatory response syndrome (SIRS) fuelling SAP [7, 8]. Such an excessive inflammatory response can increase permeability, as represented by the systematic development of organ dysfunction, which can include the gut, lung, renal, and hepatic organs [9]. Increased permeability of intestinal mucosa can lead to intestinal bacterial translocation, and lead to secondary infection of the pancreatic and/or peripancreatic tissues [8].

SAP development and the marked change in the immune response is thought to play a central role in the development of SIRS, multiple organ dysfunction, secondary infection, and subsequent septic complications [10]. Recent studies have focused on the cytokine network and immune dysfunction as key pathological mechanisms of SAP. The focus of these studies was excessive inflammatory immune

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response-mediated pathological damage and cell-mediated immunity [11, 12]. However, few studies have investigated patient immunity with regard to secondary SAP infection in the clinic.

This study was undertaken to examine immune system changes in patients with SAP as indicated by plasma pro- and anti-inflammatory cytokines and the immune response of peripheral blood mononuclear cells (PBMC).

Materials and methods

Patients

Seventy-nine adult patients with SAP were recruited between July 1, 2007 and December 30, 2009. All patients were admitted directly to the National Medical Center of Biliopancreatic Diseases at the Nankai Clinical School of Tianjin Medical University. All patients met the severe disease criteria proposed at the International Symposium on Acute Pancreatitis [13]. The Balthazar CT severity index was applied to the initial contrast-enhanced CT. The initial severity of pancreatitis was assessed by using the Acute Physiology and Chronic Health Evaluation II (APACHE II) [14], Ranson scores, and Balthazar scores, and severe pancreatitis was diagnosed as an inclusion criterion with an APACHE II score of eight or higher, a Ranson score of four or higher, and Balthazar scores of four or higher. Patients who had autoimmune disease, immunodeficiency disease, malignancy, surgical interference, or pregnancy, or had received hormone or immunosuppressive agents within the last 3 months, were excluded from the study.

SAP secondary infections were confirmed by bacterial culture, blood culture, and/or computed tomography-guided fine needle aspiration (FNA) of pancreatic or peripancreatic tissue, and/or computed tomography-guided aspiration for suspected pancreatic or peripancreatic sepsis, or large localized fluid collections [2].

Inclusion and exclusion criteria

Inclusion criteria were: age between 18 and 60 years, more than 28 days of hospitalization, and signed informed consent. Exclusion criteria were: (1) patients diagnosed with concurrent pancreatic or peripancreatic infection at admission; (2) surgery during the study period; (3) pregnant or lactating females; (4) patients with cancer; (5) critically ill patients; (6) serious organ dysfunction; (7) immunodeficiency or autoimmune disease; and (8) patients participating in another research study.

Treatment

All patients were treated with standard Chinese protocols in our institution according to a standardized interdisciplinary management protocol, including intravenous fluids, organ system support, nutritional support, gastrointestinal decompression, and prophylactic antibiotics (ciprofloxacin/metronidazole or imipenem/cilastatin).

We used intragastric administration of traditional Chinese medicine twice each day after admission, over the course of the study. If the patient did not need a nasogastric tube, the drug was administrated orally.

Ethics

The study was approved by the hospital ethics committee. Patients or their relatives were given printed information, and signed informed consent was obtained before entry into the study.

Data collection

Data were collected from all patients prospectively. The data included gender, age, pancreatitis etiology, severity score, and demographic data. Biochemical data included the percentages of CD4+, CD8+, natural killer (NK), and HLA-DR+ cells and B lymphocytes, the CD4+/CD8+ ratio, and the serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), and interleukin-4 (IL-4). Peripheral venous blood samples (5 mL) were obtained from patients upon admission and on days 1, 7, 14, and 28 using a strict aseptic technique. One 2 mL aliquot of venous blood was obtained using BD Multitest IMK kit (BD Corporation, Franklin Lakes, NJ, USA), and stained with FITC anti-human CD14, PE anti-human HLA-DR, PE mouse IgG2b isotype control (all from eBioscience Corporation, San Diego, CA, USA), and examined using a FACSort flow cytometer (BD Corporation) and CellQuest software. Another 3 mL was used to detect inflammatory factors (TNF-α, IL-6, IL-10, and IL-4) using established enzyme-linked immunosorbent assay (ELISA) kits (Bio-Rad Laboratories, Hemel Hempstead, UK).

Statistical analysis

Comparisons of continuous and categorical variables between two groups used the nonparametric Mann–Whitney U test and the χ^2 test with Yates correction, respectively. Data were analyzed using SPSS 11 (Chicago, IL, USA). Continuous data are presented as the mean ± standard error of the mean. Correlations were evaluated with the Spearman rank test. $P < 0.05$ was considered statistically significant.

Results

There were 79 patients in our study and 15 acquired a secondary infection. Data on gender, age, etiology, APACHE II score, and Balthazar scores at admission in the two groups are given in Table 1. There were no significant differences in age, gender, or etiology between the two groups. Based on the APACHE II and Balthazar scores, the severity at admission was different between the two groups.

Time required for SAP patients to acquire a secondary infection

Fifteen of the 79 patients had SAP with secondary infection. The time for secondary infection to appear is provided in Table 2. The time for secondary infection of peripancreatic or pancreatic necrosis was 7–20 days.

Comparison of PBMC

The PBMC levels in the infected group were quite different from the non-infected group, with a higher percentage of CD4+ and HLA-DR+ cells on days 1, 7, 14, and 28, higher than the percentage of CD8+ and NK cells on days 14 and 28, but exhibiting a lower CD4+/CD8+ ratio and B lymphocyte levels (Tables 3, 4, 5, 6, 7, 8). For SAP patients, the percentage of CD4+ cells increased significantly on day 7 and but was markedly depleted by 28 days in the infected group ($P < 0.05$, Table 3). The percentage of CD8+ cells was higher in the infected group at 28 days compared with the other time points ($P < 0.05$, Table 4). The CD4+/CD8+ ratios were elevated in infected patients on days 7, 14, and 28 compared with non-infected patients, and progressively decreased ($P < 0.05$, Table 7). The

Table 1 Characteristics of SAP patients with and without secondary infection

	Infected ($n = 15$)	Non-infected ($n = 64$)	P
Gender (M/F)	7/8	30/34	NS
Age (years)[a]	43.5 ± 11.6	40.2 ± 13.8	NS
Etiology (n)			
Cholelithiasis	6	25	
Alcohol	4	17	
Hyperlipidemia	3	13	
Others	2	9	NS
APACHE II score[a]	9.8 ± 6.9	8.6 ± 6.2	<0.05
Balthazar scores[a]	5.5 ± 2.5	4.3 ± 1.5	<0.05

NS not significant

[a] Mean ± SEM

Table 2 Time for secondary infection to occur in SAP

Time (days)	n	Percentage (%)
1–6	0	0
7–13	3	3.80
14–20	12	15.19
21+	0	0

Table 3 Comparison of percentage change in CD4+ cells (mean ± SEM)

	1 day	7 days	14 days	28 days
Infected	39.6 ± 7.4	47.0 ± 9.8	46.6 ± 11.8	20.3 ± 5.0
Non-infected	36.5 ± 8.6	43.4 ± 4.0	42.7 ± 12.8	40.5 ± 10.3
P	<0.05	<0.05	<0.05	<0.05

Table 4 Comparison of percentage change in CD8+ cells (mean ± SEM)

	1 day	7 days	14 days	28 days
Infected	24.6 ± 8.1	22.3 ± 11.3	25.6 ± 8.3	47.3 ± 12.9
Non-infected	26.4 ± 10.2	24.6 ± 5.6	23.6 ± 6.7	31.5 ± 21.9
P	<0.05	<0.05	<0.05	<0.05

Table 5 Comparison of percentage change in NK cells (mean ± SEM)

	1 day	7 days	14 days	28 days
Infected	7.4 ± 4.6	7.5 ± 4.7	14.6 ± 9.9	17.0 ± 9.6
Non-infected	13.3 ± 9.0	9.9 ± 9.2	12.4 ± 11.9	9.5 ± 3.5
P	<0.05	<0.05	<0.05	<0.05

Table 6 Comparison of percentage change in B lymphocytes (mean ± SEM)

	1 day	7 days	14 days	28 days
Infected	26.2 ± 3.3	19.5 ± 8.9	13.8 ± 7.8	5.7 ± 2.1
Non-infected	19.1 ± 12.4	19.7 ± 6.8	15.4 ± 8.2	15.5 ± 4.9
P	>0.05	>0.05	<0.05	<0.05

Table 7 Comparison of percentage change in CD4+/CD8+ ratio (mean ± SEM)

	1 day	7 days	14 days	28 days
Infected	1.83 ± 0.66	2.88 ± 2.39	1.77 ± 0.67	0.43 ± 0.06
Non-infected	1.56 ± 1.31	1.85 ± 0.72	1.95 ± 0.49	1.87 ± 0.88
P	<0.05	<0.05	<0.05	<0.05

Table 8 Comparison of percentage change in HLA-DR+ cells (mean ± SEM)

	1 day	7 days	14 days	28 days
Infected	85.82 ± 8.32	87.27 ± 14.84	89.21 ± 17.10	88.30 ± 14.10
Non-infected	77.17 ± 4.62	63.42 ± 5.64	56.82 ± 30.92	39.75 ± 27.09
P	<0.05	<0.05	<0.05	<0.05

Table 9 Comparison of TNF-α changes (pg/ml, mean ± SEM)

	1 day	7 days	14 days	28 days
Infected	62.33 ± 25.27	76.87 ± 22.62	73.69 ± 25.83	30.66 ± 8.78
Non-infected	45.53 ± 14.40	52.35 ± 18.72	45.47 ± 11.02	42.52 ± 14.97
P	<0.05	<0.05	<0.05	<0.05

CD4+/CD8+ ratio was markedly depleted by 28 days in the infected group ($P < 0.05$, Table 7). The percentage of B lymphocytes progressively decreased in the infected group ($P < 0.05$, Table 6). In contrast, B lymphocyte levels were maintained at a relatively high and stable level in the non-infected group ($P < 0.05$, Table 6). HLA-DR levels were significantly higher in the infected group on days 7, 14, and 28 ($P < 0.05$, Table 8). In contrast, HLA-DR levels were markedly depleted by 28 days in the non-infected group ($P < 0.05$, Table 8). The HLA-DR+ cells were maintained at a relatively low and stable level in the non-infected group ($P < 0.05$, Table 8).

Comparison of inflammatory factors

Cytokine levels in the infected group were quite different from the non-infected group, with elevated TNF-α and IL-6 on days 1, 7, and 14, and decreased levels on day 28. IL-10 and IL-4 were elevated on day 1 but reduced on days 7, 14, 28 ($P < 0.05$; Tables 9, 10, 11, 12; Fig. 1). In infected patients, TNF-α peaked on day 7 but was markedly depleted by day 28, with similar levels on days 7 and 14 ($P > 0.05$, Table 9). In the infected group, IL-6 peaked on day 14 but was depleted by day 28, with similar levels on days 7 and 14 ($P > 0.05$, Table 10). The anti-inflammatory cytokines IL-10 and IL-4 increased slowly on days 7 and 14, peaking on day 14. In contrast, the pro-inflammatory and anti-inflammatory cytokines peaked on day 7 and gradually decreased until day 28 (Tables 11, 12).

Discussion

SAP is one of the most serious pancreatic diseases and can follow two natural courses [1, 15]. The first course is characterized by SIRS, resulting from the release of inflammatory mediators. The second course appears 1–3 weeks following infection and is dominated by pancreatic necrosis, which can lead to sepsis-related complications [16], and occurs in 40–70 % of SAP patients [15, 17]. SAP pathogenesis is complicated, but immune damage resulting from the cytokine network is one of the key pathological mechanisms of SAP [18]. In early-stage SAP, hypercytokinemia plays a dominant role in SIRS development and triggers an excessive immune response [19, 20]. In later-stage SAP, the excessive inflammatory response is counteracted by a systemic release of anti-inflammatory mediators, followed by immunosuppression [19–21].

Researchers have found that inflammatory mediators contribute to early SAP causing systemic epithelial barrier dysfunction [22] and increased vascular endothelial permeability [23]. The gut fuels SAP [24], which activates development of a local or systemic inflammation response and secondary infection of pancreatic necrosis [22, 25].

TNF-α and IL-6 are the key proinflammatory cytokines mediating SAP. The excessive release of inflammatory mediators during SAP is the primary reason for secondary infection, which increases intestinal mucosa permeability, aggravates intestinal bacteria, and ultimately leads to death [26]. In contrast, the release of anti-inflammatory factors, such as IL-4 and IL-10, compensate for the inflammatory response, and increase during excessive inflammatory responses in SAP [27].

Cellular immunity may play a fundamental role in SAP and abnormal cellular immunity may be related to the outcome [28]. Immunological events are believed to be involved in SAP pathogenesis, although how immune dysfunction causes SAP is unclear [29]. Cell-mediated immunity is an important component of the immune system, and the percentages of T-helper (CD4+), T-suppressor (CD8+), NK, and HLA-DR+ cells and B lymphocytes, and the CD4+/CD8+ ratio in PBMC reflect immune status. The density of CD4+, CD8+, NK, and

Table 10 Comparison of IL-6 changes (pg/ml, mean ± SEM)

	1 day	7 days	14 days	28 days
Infected	116.9 ± 27.98	129.67 ± 28.94	132.87 ± 25.07	50.07 ± 25.55
Non-infected	98.92 ± 31.06	115.56 ± 27.44	85.58 ± 19.67	80.65 ± 25.09
P	<0.05	<0.05	<0.05	<0.05

Table 11 Comparison of IL-10 changes (pg/ml, mean ± SEM)

	1 day	7 days	14 days	28 days
Infected	107.2 ± 25.43	152.04 ± 38.37	157.57 ± 47.57	149.28 ± 36.68
Non-infected	124.2 ± 34.79	131.58 ± 37.83	109.78 ± 22.97	106.21 ± 26.76
P	<0.05	<0.05	<0.05	<0.05

Table 12 Comparison of IL-4 changes (pg/ml, mean ± SEM)

	1 day	7 days	14 days	28 days
Infected	47.27 ± 19.17	63.33 ± 17.41	66.52 ± 20.29	59.34 ± 17.85
Non-infected	54.56 ± 27.27	59.77 ± 21.47	40.89 ± 15.00	37.90 ± 18.57
P	<0.05	<0.05	<0.05	<0.05

HLA-DR+ cells and B lymphocytes, and the ratio of CD4+/CD8+ cells in the periphery change in the course of SAP [30, 31]. There are at least two major CD4+ T-cell subsets, one which secretes IFN-α and IL-6, and one which produces IL-4 and IL-10 [32].

In summary, we describe a cohort of SAP patients with secondary infection treated by a combination of traditional Chinese medicine and Western medicine. The time to secondary infection for peripancreatic or pancreatic necrosis was 7–20 days. Although etiology, age, and gender were similar between the infection groups and the non-infected groups, the severity (based on APACHE II, Ranson scores, and Balthazar scores) and immunity at admission were quite different. The PBMC levels in the infected group were quite different from the non-infected group.

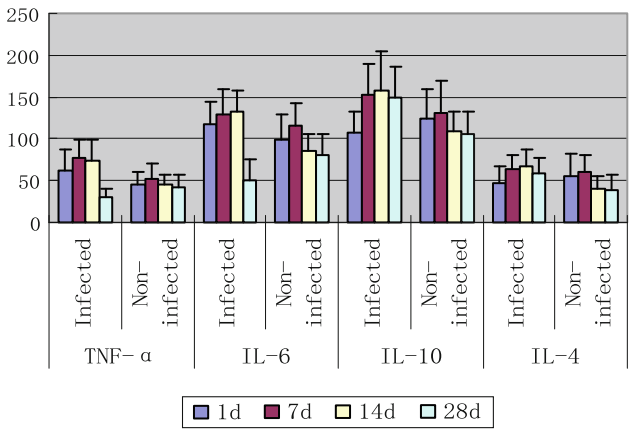

Fig. 1 Comparison of the changes in inflammatory factors between the two groups (pg/ml, mean ± SEM)

Our findings suggest that the severity of SAP is associated with bacterial contamination of pancreatic necrosis. SAP with necrosis infection is likely to show an aggressive course, during which severity increases. Our study showed that the excessive inflammatory response peak was 7 days and/or 14 days, whereas the time for secondary infection was 7–20 days.

Our results show that increased pro-inflammatory factors IL-6 and TNF-α and over-activation of CD4+, HLA-DR+, and NK cells and B lymphocytes were associated with secondary infection. The excessive release of anti-inflammatory cytokines IL-10 and IL-4 and CD8+ cells leads to a pro- and anti-inflammatory cytokine imbalance in late-phase SAP. Infection is caused mainly by an excessive immune response and subsequent immune dysregulation. Evidence has accumulated that an excessive immune response is counteracted by the systemic release of anti-inflammatory mediators, and an immunosuppression that is thought to contribute to secondary infections [33, 34]. Liu et al. [11] found that the levels of T-lymphocyte subsets in the combined traditional Chinese medicine and Western medicine treatment group were quite different from the conventional Western medicine treatment group. Shen et al. [12] reported that cytokine levels in the infected group were different from the non-infected group, with elevated TNF-α and IL-6 on days 1, and 7, and reduced levels on day 14. IL-10 and IL-4 increased on days 7 and 14.

In summary, an early excessive immune response and subsequent immune deficiencies are closely related to secondary infection from SAP. Future large-scale, high-quality, multicenter trials are required to clarify immune system dynamics throughout the course of SAP.

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