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The Type and Frequency of Infections Occurring in Collagen Tissue Diseases

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Abstract: Corticosteroids, widely used in the treatment of collagen tissue diseases, increase the number of neutrophils and decrease the total numbers of lymphocytes, monocytes, eosinophils and basophils. In addition, corticosteroids alter important functional activities of both lymphocytes and monocytes. They suppress the bactericidal activities of phagocytes. In this manner, the resistance to infections is reduced. Cytotoxic drugs can have profound effects on the production and function of both phagocyte cells and lymphocytes.

We followed up 115 patients with collagen tissue disease for two years and 22 of them had infections. Eight of these 22 patients had urinary tract infection, six had lung infection, four had upper respiratory tract infections, two had wound infections, and one had intestinal infestation. All of the patients were

treated with appropriate antimicrobial agents but two patients died due to septicemia.

Infection remains a significant cause of morbidity and mortality in patients with collagen tissue diseases. Consequently, the early diagnosis and treatment of infections are very important for the successful medical management of these patients. The intensity of immunosuppressive therapy is the dominant risk factor for infection in these patient populations. Because the manifestations of infection in patients with collagen tissue diseases are highly variable, the clinician must always be alert to the possibility of infection even if the clinical presentation is highly suggestive of an exacerbation of the underlying disease.

Key Words: Collagen tissue diseases, Infection, Corticosteroid, Cytotoxic drugs.

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Introduction

The most important function of the immune system is to protect the host against harmful microorganisms. Defense mechanisms include the physical barriers of the skin and mucosal membranes, the complement system, prostaglandins, cytokines, lysozymes, natural killer (NK) cells and phagocytic cells. The iatrogenic destruction of anatomical barriers causes many bacterial and fungal infection agents to enter the host. Immunosuppressive agents used in collagen tissue diseases can lead mucositis and sometimes to cystitis (1).

Phagocytic cells (e.g. neutrophils, macrophages) have a very important function in the phagocytosis of immune complexes and infectious agents. When infectious agents pass the primary barriers, polymorphonuclear leucocytes provide immunity against potential pathogens such as gram (+) and gram (-) bacteria and fungal agents. Monocytes and macrophages in the reticuloendothelial system

provide an important support for the elimination of viruses, mycobacteria, and certain viruses that neutrophils do not affect (2).

Neutropenia is the most serious problem in collagen tissue diseases. Neutropenia is generally associated with immunosuppressive therapy. Sepsis risk increases when the neutrophil count falls below 500/mm³ and remains in this state for 20 days. The immunological response of the host to the microorganisms occurs by means of immunoglobulins and T lymphocytes. The antibody-bacteria complexes are cleaned either by phagocytes or by macrophages in the reticuloendothelial system (1).

The complement system is a potent biological system in the host defense. Among the biological effects of complements are chemotaxis and anaphylaxis, opsonization and phagocytosis of microorganisms, the clearance of immune complexes from circulation and an increase in vascular permeability (3).

Infection is of special significance in collagen tissue diseases. Patients with collagen tissue disease become sensitive to infections because of the use of corticosteroids and/or immunosuppressive drugs in the treatment. Corticosteroids inhibit neutrophils from migrating to the inflammation site, from adhering to the vascular endothelium and from exerting bactericidal effects. Using a high dose steroid can inhibit the production of immunoglobulins (4). It can also cause lymphocyte, monocyte, eosinophil and basophil counts to decrease. In addition, it suppresses the antibacterial activities of phagocytes. It causes the lymphoid subpopulation to decrease, especially in T lymphocyte counts. Its effect on B lymphocytes is less than that on T cells. The administration of a high dose corticosteroid decreases the production of Ig G and Ig A.

Cytotoxic drugs cause neutropenia and affect the counts of T and B lymphocytes. Cyclophosphamide, which is a potent immunosuppressive drug, influences primarily the B lymphocytes. However, although it influences all cells in bone marrow, it does not often cause leukopenia (5). Azathioprine decreases both T and B lymphocytes in long term administration. It suppresses the synthesis of immunoglobulins. It does not influence the neutrophil function. It can cause bone marrow suppression (4). Methotrexate has an evident immunosuppressive effect.

It suppresses the synthesis of antibodies and the primary and secondary immune response (6). The predominant immunological defects and the pathogen microorganisms caused by drugs administered in the treatment of collagen tissue diseases are shown in Table 1.

As mentioned above, the risk of infection increases in patients with collagen tissue diseases. This situation is important because of the activation of diseases. In this article, we discuss the cause and results of infection in collagen tissue disease in the light of the literature.

Materials and Methods

This study included 115 patients with collagen tissue disease who were followed up between 1996 and 1998. Infection was detected in 22 (19%) of these patients during the follow-up period. The average age of the patients was 43 (18-65). Twelve of the patients with infection had SLE, eight had RA, and two had MCTD. For the patients with flares in clinical findings and symptoms, throat, urinary and blood cultures, as well as sputum cultures (if the patient expectorated sputum) were performed.

The patients were treated in accordance with the results of the cultures and antibiograms. In addition, the

Table 1. Evident immunological defects and pathogens associated with certain drugs being administered in the treatment of collagen tissue diseases.

Abnormality	Drugs	Bacteria	Fungus	Protozoa	Virus
Qualitative defect of phagocytic function or neutropenia	CS CYC AZT	Gram (+) Gram (-) bacteria	Candida Aspergillus		
Defective cell-mediated immunity	CS CYC AZT MTX CY-A	Mycobacteries Listeria Salmonella Nocardia	Histoplasmosis Coccidioides Cryptococcus	P.C. Toxo Strong. stercoralis	CMV EBV VZV
Defective humoral immunity	CYC CS AZT	S. Pneumonia H. Influenzae			

CMV: Cytomegalovirus EBV: Ebstaine-Barr virus VZV: Varicella-Zoster Virus
 CS: Corticosteroid AZT: Azathioprine CYC: Cyclophosphamide
 MTX: Methotrexate CY-A: Cyclosporine -A P.C: Pneumocystis Carinii

treatment of the underlying disease was continued. All the patients with SLE in whom infection developed were administered corticosteroid. While the patients with RA were administered methotrexate, sulfasalazin and nonsteroid antiinflammatory drugs, those with MCTD were administered corticosteroid and nonsteroid antiinflammatory drugs.

Results

In four of the patients with SLE in whom infection was detected, more than one infection occurred and there

was infection in only one site in eight patients developing infection. In two of the patients with RA, infection developed in more than one site while in six of them infection developed in only one site. There was infection in only one site in patients with MCTD. Infection was detected mostly in the urinary system, followed by lung infection and upper respiratory infection. Sepsis was detected in eight patients. Improvements were seen in clinical findings and symptoms in other patients after treatment of the infection. The distribution of patients, agents of infections, and infection sites of patients with collagen tissue disease developing infection are shown in Table 2.

Table 2. Agents associated with infection and sites in collagen tissue diseases.

PATIENT	SEX	AGE	DIAGNOSIS	INFECTION SITE	AGENT
1	F	33	RA	Throat	<i>S. epidermidis</i>
				Blood	<i>S. epidermidis</i>
2	F	38	RA	Vagina	<i>C. albicans</i>
3	F	58	RA	Lung	<i>S. aureus</i>
4	F	57	RA	Lung	<i>S. pneumonia</i>
5	M	69	RA	Urinary system	<i>S. aureus</i>
6	F	60	SLE	Urinary system	<i>E. coli</i>
7	F	30	SLE	Colon	<i>E. histolytica</i>
8	F	61	RA	Lung	<i>S. pneumonia</i>
				Blood	<i>C. albicans</i>
					<i>E. coli</i>
9	F	30	SLE	Throat	<i>C. albicans</i>
				Urinary system	<i>E. coli</i>
				Blood	<i>S. aureus</i>
				Joint	<i>S. aureus</i>
10	F	55	SLE	Urinary system	<i>E. coli</i>
11	F	21	SLE	Urinary system	<i>E. coli</i>
12	F	67	RA	Blood	<i>Proteus spp.</i>
13	F	42	SLE	Lung	<i>P. aeruginosa</i>
14	F	18	SLE	Throat	<i>C. albicans</i>
				Blood	<i>S. epidermidis</i>
15	F	21	MCTD	Urinary system	<i>Klebsiella</i>
16	F	20	SLE	Joint	<i>S. aureus</i>
				Blood	<i>S. aureus</i>
17	M	33	MCTD	Joint	<i>S. aureus</i>
				Blood	<i>S. aureus</i>
18	F	35	SLE	Lung	<i>Pseudomonas spp.</i>
				Blood	<i>S. epidermidis</i>
19	F	23	SLE	Urinary system	<i>E. coli</i>
20	M	43	SLE	Urinary system	<i>E. coli</i> + <i>Klebsiella</i>
21	M	67	RA	Lung	<i>S. pneumonia</i>
22	F	49	SLE	Urinary system	<i>S. aureus</i>

Discussion

Corticosteroids and immunosuppressive drugs are of indispensable importance in the treatment of collagen tissue diseases. Before the use of these drugs, there were high levels of morbidity and mortality. Notable decreases have been achieved with these drugs. Although these drugs have many beneficial effects, they also have unignorable degrees of side effects, of which infection is significant. The development of infection in these patients is a triggering factor in the exacerbation of the disease. Infection is also a major cause of morbidity in patients with collagen tissue diseases (7-9).

Bradley et al. (10) investigated the risks of infection in patients with vasculitis who were being administered cyclophosphamide. The total follow-up time of the patients was 201 months and 17 infections were detected during this period. They detected 5 lung infections, 4 skin infections, and 3 urinary tract infections. The other infection sites detected were the peritoneum, gastrointestinal system, blood, paranasal sinus, knee and bursa of olecranon. In this study, the infectious agents were gram (+) and (-) bacteria, anaerobic bacteria, candida, P. Carinii and herpes. However, the most common agents were enterobacteria, pseudomonas and staphylococcus. Many agents were detected in 4 patients. Two patients died during follow up because of pneumonia.

Duffy et al. (11) followed up 81 patients with SLE for 5 years. During this time they detected 53 incidents of infection, 34 of which were serious. The serious infections were pneumonia, bacteriemia, septic arthritis and abscesses. The most common microbial agents were gram (+) and (-) bacilli and candida. In their study, other minor infections included urinary tract, vaginal, skin and mucocutaneous infections.

We detected infection in 22 (16%) of the 115 patients with collagen tissue disease included in this study. Infection was treated according to the results of cultures and antibiograms. Two (9%) of the patients with sepsis died. Tuberculosis infection was not detected in any of these patients. Shyam et al. (12) followed up 309 patients in their study. They detected infection in one or more sites in 82 (26.5%) cases. Tuberculosis infection was often found. In addition, Koh et al. (13) followed up patients with collagen tissue disease for a period of 4 years. Sixty-seven of them died. Twenty-seven (40.3%) of them died of infection, 30 (44.8%) died of SLE, and 4

(5.9%) died of malignancy. These results indicate that infection plays an important role in the mortality and morbidity of patients with collagen tissue disease. In another study supporting this view, Jacobsen et al. (14) followed up 513 patients with SLE. One hundred twenty-two of them died: 25% of the death rate was infection, 19% was active SLE and 16% end-stage organ failure. Furthermore, Cerceva et al. (15), in a multicenter study, followed up 1000 patients with SLE for 5 years. Infection developed in 27% of them; 5.4% of the 1000 patients died. Infection was the primary cause of death with a rate of 28.9%. The infection rates in these studies are close to those obtained in our cases. We think that the difference results from the number of patients.

Lee et al. (16) followed up 110 patients with SLE for 4.5 years. In this period, they encountered a 26.3% proportion of infection; 10.1% of them were major infections. Staples et al. (17) followed up 23 patients with SLE in hospital for 4 weeks and reported a 56.5% proportion of infections. In a meta-analysis carried out, while infections were detected to be 12.7% of the proportion of 2111 patients administered corticosteroid, this proportion was reported to be 8% in 2087 control cases (4). Hoffman et al. (5) detected a total of 140 serious infections in 73 of 158 patients with Wegener Granulomatosis who had been administered corticosteroid and cyclophosphamide. Thirty-nine percent of these infections were pneumonia. The infection rate was detected to be 16% in patients receiving merely cytotoxic drugs. In another study, major infection was reported in 2 of 19 patients receiving azathioprine.

Several studies have reported risks of infection ranging from 0 to 20% in methotrexate receivers. The most frequent opportunistic infections in methotrexate receivers are P. Carinii pneumonia and Z. Zoster. In one study, P. Carinii pneumonia was detected in 5 (7%) of 68 patients with Wegener Granulomatosis receiving methotrexate and corticosteroid (6).

These studies, and ours, have demonstrated that infection is of special significance in collagen tissue diseases. These patients become sensitive to infections because of being administered corticosteroid and/or immunosuppressive drugs during treatment. Indeed, infection also causes the activation of collagen tissue diseases. Therefore, we must be careful about the development of infection during the follow-up period, and must treat these patients effectively if infection develops.

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