Analysis of the Clinical Characteristics of Malignant Tumor Patients with Rheumatic Symptoms and Rheumatic Disease Combined with Malignant Tumor Patients

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Abstract: **Objective:** We study the relationship between rheumatic immune disease and malignant tumor to provide the basis for clinical diagnosis and treatment. **Methods:** We selected 53 patients who were hospitalized in our department from January 2013 to February 2020, including 26 patients with rheumatic immune disease combined with malignant tumor and 27 patients with malignant tumor with rheumatic symptoms. We retrospectively analyzed the relationship between gender, age, main clinical manifestations, tumor system distribution, metastasis rate, rheumatic immune disease type and tumor type. **Results:** Among the patients with rheumatic immune disease complicated with tumor, 26.1% were male and 66.7% were female. Among the tumor patients with rheumatic symptoms, 73.9% were male and 33.3% were female. There was a significant difference in gender composition between the two groups. Among the patients with rheumatic immune disease complicated with tumor, respiratory system tumor was the highest. Among the tumor patients with rheumatic symptoms, the incidence of hematological tumors was the highest. The distribution of tumor system was different between the two groups. The proportion of metastatic tumor in patients with rheumatic symptoms is higher than that in patients with rheumatic immune disease combined with malignant tumor. The percentage of concurrent tumor in three diseases in the same period was 0.363% for rheumatoid arthritis, 2.02% for polymyositis/ dermatomyositis and 0.24% for Sjogren's syndrome. This study shows that patients with polymyositis/ dermatomyositis are more likely to develop malignant tumors. **Conclusion:** There were significant differences in gender composition, distribution of tumor system and the proportion of metastatic tumor between patients with rheumatic immune disease complicated with malignant tumor and patients with rheumatic symptoms, and malignant tumor was more common in patients with polymyositis/ dermatomyositis.

Keywords: Rheumatic Immune Disease; Malignant Tumor

Introduction

Rheumatic immune disease is a common clinical disease, its etiology is still unknown, its clinical manifestations are diverse, it often damages multiple systems, and the patient's condition is unstable and has a trend of continuous aggravation. Current research shows that the main pathogenesis of rheumatic immune disease is the abnormality of the immune system of the body, which leads to the immune response to the autoantigen, causing the damage of the own tissue. Many studies have shown that the main causes of death of patients with rheumatic immune diseases are infection, respiratory diseases, cardio-cerebrovascular diseases and malignant tumors. In recent years, the number of deaths caused by malignant tumors in patients with rheumatic immune diseases has increased significantly [1]. Autoimmune system can eliminate tumor cells or inhibit their growth through various ways. When the immune function is abnormal, it can cause tumor cells to escape immune surveillance and induce tumor [2]. Many kinds of rheumatic immune diseases, such as rheumatoid arthritis,

polymyositis/dermatomyositis, Sjogren's syndrome, systemic lupus erythematosus and so on, can be associated with malignant tumors. Malignant tumors have many extra-tumor clinical manifestations, such as bone, joint and muscle pain, polymorphic rash, repeated fever, etc. These symptoms are similar to the clinical manifestations of rheumatic immune disease. Some of them are the first symptoms of malignant tumors, and may also be signs of recurrence or metastasis of malignant tumors [3]. In our study, 53 patients with rheumatic immune disease combined with malignant tumor or malignant tumor with rheumatic immune disease symptoms as the main manifestation were collected. By analyzing the clinical characteristics of these patients, we expounded the relationship between rheumatic immune disease and malignant tumor. Our aim is to reduce the misdiagnosis rate of patients with malignant tumors associated with rheumatic immune diseases.

1. Data and methods

1.1 Research object

We collected the clinical data of 6032 patients. These patients were hospitalized in our department from January 2013 to February 2020. We selected 53 patients for this study. These patients were finally diagnosed as malignant tumors. Some patients were diagnosed with rheumatic immune disease, and the other patients had similar initial manifestations to rheumatic immune disease. The patients were divided into two groups. 1. Rheumatic immune disease group: patients with rheumatic immune disease and malignant tumor. 2. Non-rheumatic immune disease group: malignant tumor patients with initial clinical symptoms similar to rheumatic immune disease. Inclusion criteria: 1. The diagnosis of rheumatic immune disease meets the corresponding diagnosis and classification criteria; 2. Malignant tumors were diagnosed by clinical manifestations, physical signs, imaging and histopathological examination. We retrospectively analyzed the relationship between gender, age, main clinical manifestations, tumor type, incidence of tumor metastasis, type of rheumatic immune disease and tumor type.

1.2 Data analysis

The medical records were recorded with Excel software, the database was established, and analyzed with spss 21.0 statistical software. Continuous variables are expressed as mean ± standard deviation (SD). Qualitative variables are expressed as percentages. $P<0.05$ was considered statistically significant.

2. Results

2.1 Comparison of gender and age of patients in the two groups

There were 26 patients with rheumatic immune disease and malignant tumor, ranging from 33 to 79 years old. There were 27 patients with malignant tumor with rheumatic symptoms, ranging from 33 to 87 years old. The average age of patients in the two groups was 60.8 years old. There was no statistical difference in the average age of onset (Table 1 and Table 2). There was no statistical difference in the age stratification between the two groups (Table 3).

Table 1 Age of onset

	Rheumatism or not	Number of cases	Average value	Standard deviation	Mean standard error
Age	Yes	26	60.808	11.6482	2.2844

of onset	No	27	60.852	13.8083	2.6574

Table 2 Independent sample test

		Levin's variance equivalence test		Mean equivalence t-test						
		F	significance	t	Degree of freedom	Significance (two-tailed)	Mean difference	Standard error difference	Difference 95% confidence interval	
									Lower limit	Upper limit
Age of onset	Assumed equal variance	1.144	.290	-.013	51	.990	-.0442	3.5157	-7.1022	7.0139
	Equivariance is not assumed	-.013		50.146	.990	-.0442	3.5043	-7.0823	6.9940	

Sig>0.05, the total variance of the two samples is the same; p> 0.05, there was no difference in the age of onset between the two groups.

Table 3 Cross table of age stratification * rheumatism

			Rheumatism or not		Sum
			No	Yes	
Age stratification (age)	18-45	Count	5_a	3_a	8
		Percentage of age stratification	62.5%	37.5%	100.0%
	46-69	Count	26_a	34_a	60
		Percentage of age stratification	43.3%	56.7%	100.0%
	>69	Count	27_a	18_a	45
		Percentage of age stratification	60.0%	40.0%	100.0%
Sum		Count	58	55	113

	Percentage of age stratification	51.3%	48.7%	100.0%
Each subscript letter indicates whether there is a subset of rheumatic disease categories. At the. 05 level, there is no significant difference between the column proportions of these categories.				

Chi-square test

	Number	Degree of freedom	Progressive significance (bilateral)	Accuracy significance (bilateral)
Pearson chi-square	3.289[a]	2	.193	.192
Likelihood ratio	3.308	2	.191	.192
Fisher's exact test	3.270			.192
Number of valid cases	113			

a. 2 cells (33.3%) have an expected count less than 5. The minimum expected count is 3.89.

P> 0.05, there is no significant difference between the two groups in age stratification.

Of the 26 patients with rheumatic immune disease and malignant tumor, 6 were male and 20 were female, with male patients accounting for 26.1% and female patients accounting for 66.7%. Among the 27 patients with malignant tumors with rheumatic symptoms as the main manifestation, 17 were male and 10 were female, with 73.9% of male patients and 33.3% of female patients. There were significant differences in gender composition between the two groups (Tables 4 and 5).

Table 4 Sex * Presence or absence of rheumatic crosstabs

			Rheumatism or not		Sum
			No	Yes	
Gender	Male	Count	17	6	23
		Percentage of sex	73.9%	26.1%	100.0%
	Female	Count	10	20	30
		Percentage of sex	33.3%	66.7%	100.0%
Sum		Count	27	26	53
		Percentage of sex	50.9%	49.1%	100.0%

Table 5 Chi-square test

	Number	Degree of freedom	Progressive significance (bilateral)	Precision significance (bilateral)	Precision significance (unilateral)
Pearson chi-square	8.578[a]	1	.003		
Continuity correction [b]	7.031	1	.008		
Likelihood ratio	8.862	1	.003		
Fisher's Exact Test				.005	.004
McNimar test				.[c]	

Number of valid cases	53				
A. The expected count of 0 cells (0.0%) is less than 5. The minimum expected count is 11.28.					
B. Calculation only for 2x2 tables					
C. Both variables must have the same category value.					

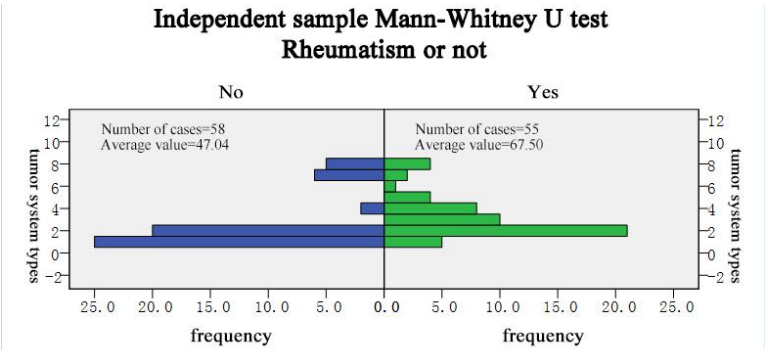
P=0.000<0.05, the gender composition of the two groups is significantly different

2.2 Comparison of tumor types between two groups of patients

26 patients with rheumatic immune disease combined with malignant tumor, including 9 cases of respiratory system tumor (8 cases of lung cancer, 1 case of nasopharyngeal cancer), 4 cases of hematological system tumor (1 case of T-lymphocyte leukemia, 2 cases of lymphoma, 1 case of multiple myeloma), 4 cases of breast cancer cancer, 4 cases of digestive system tumor (1 case of colon cancer, 1 case of pancreatic cancer cancer, 1 case of liver cancer, 1 case of rectal cancer), 2 cases of reproductive system tumor (1 case of endometrial cancer, 1 case of cervical cancer), 1 case of endocrine system tumor (thyroid cancer) One case of urinary system tumor (renal cancer) and one case of metastatic cancer (unknown primary focus).

There were 27 cases of malignant tumor patients with rheumatic symptoms as the main manifestation, including 13 cases of hematological system tumor (6 cases of lymphoma, 7 cases of multiple myeloma), 9 cases of respiratory system tumor (8 cases of lung cancer, 1 case of nasopharyngeal cancer), 2 cases of urinary system tumor (prostate cancer), 1 case of digestive system tumor (pancreatic cancer), and 2 cases of metastatic tumor (the primary focus is unknown).

There were differences in tumor system distribution between the two groups. Among the patients with rheumatic immune disease and tumor, the incidence of respiratory system tumor is the highest, followed by hematological system tumor, digestive system tumor and breast cancer. Among the tumor patients with rheumatic symptoms as the main manifestation, the proportion of blood system tumors is the highest, followed by respiratory system tumors (Figure 1).



sum	113
Mann-Whitney U	2, 172. 500
Wilcockson W	3, 712. 500
Inspection statistics	2, 172. 500
Standard error	167. 997
Standardized test statistics	3. 438
Progressive significance (bilateral)	. 001

Column	Row	V3
Check	1	Independent sample Mann-Whitney U test
Decision	1	Reject the null hypothesis.
Significance	1	5.86999435471913E-4
Null hypothesis	1	The distribution of tumor system types was the same in the rheumatic-free category.

TYPES	TYPES	MEANS	sum(COUNTS)
Yes	Yes	1	5
Yes	Yes	2	21
Yes	Yes	3	10
Yes	Yes	4	8
Yes	Yes	5	4
Yes	Yes	6	1
Yes	Yes	7	2
Yes	Yes	8	4
No	No	1	25
No	No	2	20
No	No	4	2
No	No	7	6
No	No	8	5

Legend:
1Hematologic tumor
2Respiratory system tumor
3Breast cancer
4Tumor of digestive system
5Tumor of reproductive system
6Endocrine system neoplasms
7Tumor of urinary system
8The primary metastatic tumor remains to be determined

There were 4 cases of metastatic tumor in patients with rheumatism and 7 cases of metastatic tumor in patients with malignant tumor mainly manifested by rheumatism. There was a statistical difference in the proportion of metastatic tumors between the two groups. The proportion of metastatic tumors in patients with malignant tumors mainly manifested by rheumatic symptoms was higher than that in patients with malignant tumors combined with rheumatological diseases. (Table 6, 7).

Table 6 Metastases * Presence of rheumatic crosstabs

			Rheumatism or not		Sum
			no	yes	
Transfer situation	No	Count	43_a	50_b	93
		As a percentage of transfer cases	46.2%	53.8%	100.0%
	Yes	Count	15_a	5_b	20
		As a percentage of transfer cases	75.0%	25.0%	100.0%
Sum		Count	58	55	113
		As a percentage of transfer cases	51.3%	48.7%	100.0%

Each subscript letter indicates the presence or absence of a subset of the rheumatic categories whose column proportions do not differ significantly from each other at the.05 level.

Table 7 Chi-square test

	number	Degree of freedom	Progressive significance (bilateral)	Accuracy significance (bilateral)	Accuracy significance (unilateral)
Pearson chi-square	5.451[a]	1	.020	.026	.017
Continuity correction [b]	4.361	1	.037		
Likelihood ratio	5.680	1	.017	.026	.017
Fisher's exact test				.026	.017
Number of valid cases	113				

a. The expected count of 0 cells (0.0%) is less than 5. The minimum expected count is 9.73.
b. Calculate only for 2x2 tables

P<0.05, the difference was statistically significant, and the percentage of metastasis was different between the two groups.

2.3 The first clinical manifestation of patients with rheumatic immune disease and malignant tumor

We observed the following initial clinical manifestations in patients with rheumatic immune disease combined with malignant tumor: 11 cases of arthralgia, 2 cases of fever, 3 cases of rash, 1 case of low back pain, 1 case of myalgia, 1 case of fever combined with arthralgia, 1 case of fever combined with myalgia, 1 case of rash combined with fever, 1 case of both hands combined with fever, 1 case of myalgia combined with myasthenia, 1 case of myalgia combined with rash, 1 case of lymph node swelling, and 1 case of granulocytopenia. We observed the following initial clinical manifestations in malignant tumor patients with rheumatism as the main manifestation. There were 5 cases of arthralgia, 5 cases of fever, 2 cases of rash, 4 cases of low back pain, 3 cases of myalgia, 1 case of chest and back pain, 1 case of anorexia, 1 case of nodular erythema, 1 case of fatigue, 1 case of fever combined with rash, 1 case of lymph node enlargement combined with fever, 1 case of myalgia combined with arthralgia, 1 case of short breath and joint pain. There was no difference in the first clinical manifestation between the two groups in this study. Because the number of cases studied in this group is small, it is still uncertain whether there are differences in the initial clinical manifestations of patients, which will be the main direction of our further research.

2.4 Relationship between the types of rheumatic immune diseases and malignant tumors

The 26 patients with rheumatic immune disease and malignant tumor in this study are the following three kinds of rheumatic immune diseases, including 11 cases of rheumatoid arthritis, 7 cases of myositis/dermatomyositis, and 3 cases of Sjogren's syndrome. A total of 3027 patients with rheumatoid arthritis, 346 patients with myositis/dermatomyositis and 1249 patients with Sjogren's syndrome were hospitalized in the same period. The percentage of concurrent tumors in the three diseases in the same period was 0.363% for rheumatoid arthritis, 2.02% for myositis/dermatomyositis, and 0.24% for Sjogren's syndrome. This study shows that myositis/dermatomyositis patients are more likely to develop malignant tumors. Of the 26 patients with rheumatic immune disease and malignant tumor, 8 patients were diagnosed with rheumatic immune disease and tumor at the same time, and 18 patients developed tumor after the diagnosis of rheumatic immune disease (1-40 years)

3. Discussion

The pathogenesis of rheumatic immune disease with malignant tumor is not clear, which may be related to the following factors. Immune abnormalities: Under normal circumstances, the abnormal protein complex on the surface of tumor cells can be recognized by the immune system to inhibit tumor growth or target tumor cells through various ways. When the immune function of the body is abnormal, the cellular immunity is defective and low, and the T cell immune monitoring function is decreased. Cancerous cells cannot be killed in time, and tumor cells escape immune surveillance to induce tumor. Shankaran et al. found that cancer cells showed an accelerated growth trend in immune deficient mice [4].

Chronic inflammation: It is well known that rheumatic immune disease is a chronic immune inflammatory disease, and patients have low immune function. Pathogenic microorganisms, etc., release a variety of inflammatory factors and mediators by inducing autoimmune reactions, causing DNA damage to tissue cells, making normal cells more susceptible to mutagenesis and causing tumors [5]. Chronic inflammation can also affect the activity of NK cells, and reduce the killing power of tumor cells. At the same time, inflammation can be used as a tumor promoter to promote the survival, proliferation Migration and invasion accelerate the growth and metastasis of tumor cells [6,7]. To sum up, inflammation is the key factor leading to the occurrence and development of tumor. Therefore, strict control of immune inflammation and reduction of infection can reduce the risk of tumor occurrence [8]. The patient's anti-tumor immune response is inhibited after the use of anti-rheumatic drugs and immunosuppressants, and the immune microenvironment after the use of drugs is also conducive to the growth of malignant tumors [9]. Some studies have shown that organ transplant patients need long-term immunosuppressive treatment, and the incidence of cancer is increasing [10].

The cause of malignant tumor after patients suffering from rheumatic immune disease is not clear, but according to the immune status of the body, it can be divided into three situations, and the three are not immutable. Direct infiltration: Rheumatic immune diseases caused by direct infiltration of tumor are mostly seen in metastatic cancer, primary tumor of synovial membrane/joint, and tumor of blood system (such as leukemia, lymphoma, etc.). In this study, one case of T-lymphocytic leukemia and two cases of lymphoma-associated rheumatic immune disease may be related to the direct infiltration of tumor cells. Paraneoplastic syndrome: some tumors with endocrine function can cause patients to have symptoms similar to rheumatic immune disease, such as arthritis, rash and myalgia. Many studies believe that this may be related to tumor immunity or autoimmunity. Tumor cells can release humoral factors, antigens and other substances. These substances can activate lymphocytes to produce autoimmune antibodies [11]. Rheumatic immune disease coexists with tumor: Stertz proposed in 1916 that the coexistence rate of inflammatory myopathy and malignant tumor is about 5% - 25%, most of which are dermatomyositis patients.

Relevant research shows that the incidence of RA combined with malignant tumor is 0.56%, which is 10% higher than that of the general population. The main tumor types are lymphoma and lung cancer. In this study, there were 11 cases of RA combined with malignant tumors, with a tumor detection rate of 0.363%. Lung cancer was the majority (4 cases), followed by reproductive system tumors. A prospective cohort study indicated that lung cancer in RA may be related to many risk factors such as interstitial lung disease, lung infection, oxidative damage, smoking, etc. [12]. Among many autoimmune diseases, inflammatory myopathy such as myositis dermatomyositis is the most closely related to tumor. Some tumors occur earlier than myositis dermatomyositis, and some occur at the same time with myositis dermatomyositis. It is also possible to develop new malignant tumors in the years or even decades of diagnosis of myositis dermatomyositis. Relevant literature reports that the detection rate of malignant tumors in PM/DM patients is about 17.05% [13], which is 5-7 times higher than that in the natural population. In this study, the detection rate of malignant tumors in PM/DM patients is 2.02%. This result may differ greatly from the report due to the small sample size and data bias. A meta-analysis showed that the risk factor of dermal PM/DM developing into malignant tumor was 4.4/2.1. The most common tumors were reproductive system tumors in women and lung cancer in men. Both of them may have gastrointestinal tumors [14]. Some studies have shown that PM/DM is closely related to the occurrence of ovarian cancer, lung cancer, pancreatic cancer, gastric cancer, colorectal cancer and lymphoma [15]. In this study, there are 7 cases of inflammatory myopathy with tumors, and the tumor detection rate is the highest, of which 2 cases are mainly lung cancer in men and 5 cases are mainly breast cancer in women. Tumors can occur at any stage of inflammatory myopathy. 35% of patients have tumors before PM/DM, 47% of patients have tumors detected at the same time or within half a year after the onset of PM/DM, and only 17% of patients have tumors after PM/DM. This study showed that the highest detection rate of tumors was 5 cases at the same time or within half a year of the onset of PM/DM. Due to the high incidence of tumor in inflammatory myopathy, PM/DM patients who are older than 50

years old, with normal muscle enzyme and positive tumor serology must be vigilant and actively look for evidence of tumor to avoid delaying the disease. PSS is a chronic autoimmune disease with lymphocytic infiltration of exocrine glands as its main manifestation. Relevant studies show that the incidence of malignant tumors in PSS patients is 1.04 to 2.6 times that of normal people matched by gender and age [16,17]. The relative risk rate of malignant lymphoma in PSS patients is 44 times that of ordinary people, and has a high incidence rate and mortality. In particular, the patients with recurrent exocrine gland enlargement, lymph node enlargement and hyperglobulinemia have a greater risk of lymphoma [18]. At the same time, the incidence of thyroid cancer, lung cancer, breast cancer, digestive tract tumor and urinary system tumor in PSS patients is higher, which may be related to the existence of secretion function of some glands and the involvement of PSS in multiple organs. Among the 3 patients with PSS in this study, 2 were lymphoma and 1 was liver cancer, which was consistent with the data reported. The incidence of malignant tumors in SLE patients reported in different literatures is very different. A multi-center study by Bernatsky et al. shows that the incidence of malignant tumors in SLE patients is 1.5 times that of the general population, and the tumor manifestations are diverse, which can involve hematological swelling, respiratory system, digestive system, urogenital system and thyroid [19]. However, Chun's research believes that SLE patients have the same risk of cancer as normal people. SLE patients in this study were diagnosed with rheumatism and malignant tumor at the same time, but due to the small number of cases, it can not be determined that SLE patients are more prone to malignant tumor than normal people.

The relationship between the time of patients suffering from tumor and the time of patients suffering from rheumatic immune disease showed significant diversity. Routine tumor screening should be carried out for patients with rheumatic immune disease who have clinical symptoms that cannot be explained by the primary disease or who have poor efficacy in routine use of hormones and immunosuppressants. Malignant tumor patients with rheumatic symptoms as the main manifestation are often misdiagnosed. Therefore, the main clinical manifestations of middle-aged and elderly patients are joint muscle pain, atypical rash or repeated fever that can not be effectively controlled by NSAIDs and hormones. When we can not clearly diagnose a certain kind of rheumatic immune disease. Whether these symptoms are intermittent or persistent, acute or chronic. We should highly suspect that the patient has malignant tumor. These clinical manifestations may be the first symptoms of the tumor, or the symptoms after the tumor has metastasized to joints, skin and other organs. It is necessary to carry out multiple and multi-site pathological examinations for such people.

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