Retrospective Investigation of Case Studies to Determine the Concurrent Malignancy Rate Associated with Microscopic Polyangiitis

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Abstract

Introduction: This retrospective study investigated the concurrence rate and clinical characteristics of recently developed malignancies with microscopic polyangiitis (MPA).

Materials and Methods: The subjects included 42 Japanese MPA cases (16 males and 26 females) that had been newly admitted to the hospital. Recent occurrences of malignancy (defined as malignancies diagnosed upon admission and up to two years prior to admission) and the presence of organ lesions were evaluated. As a control, recent occurrences of malignancy in 126 patients with rheumatoid arthritis (RA) were evaluated in a similar manner.

Results: Recently developed malignancies occurred significantly more often in the MPA group (19.0%) than in the RA group (6.3%; odds ratio (OR), 3.47 [95% CI, 1.21–9.93]; Fisher's exact test, $p = 0.029$). All MPA-associated malignancies were solid cancers, and none were from hematopoietic origin. With regard to characterization of organ lesions, MPA cases with malignancies exhibited peripheral neuropathy significantly more often (75% vs. 32.4%; OR, 6.27; 95% CI, 1.09–36.25; $p = 0.045$) and glomerulonephritis less often (37.5% vs. 82.4%; OR, 0.13; 95% CI, 0.02–0.69; $p = 0.020$) than MPA cases without malignancies. Skin lesions were observed in approximately 50% of cases, and there was no significant difference between MPA groups with and without malignancies (26.5%; OR, 2.78; 95% CI, 0.57–12.51; p value, 0.236).

Conclusion: MPA coincided with malignancies at a higher ratio than did RA. Therefore, it is recommended that those admitted for MPA should be thoroughly screened for malignancies.

Key words

MPA, malignancy, concurrent, ANCA-associated vasculitis, organ

Introduction

Collagen disease and vasculitis often coincide with malignancies. In particular, 6% of dermatomyositis cases also presented with malignancy at the time of diagnosis¹⁾. Primary vasculitis, polyarteritis nodosa, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), and IgA vasculitis also frequently coincide with malignancies^{2–5)}. In cases of AAV, immunosuppressants such as cyclophosphamide

are administered for treatment after diagnosis, and it is reported that malignancies develop more often in such cases than in the general population^{6–13)}. This may suggest that immunosuppression treatment carries an inherent risk of increased cancer rates in those with AAV. However, because little is known about the occurrence rate of malignancies at the time of diagnosis and before the onset of AAV, the causal relationship between malignancy and AAV remains in question. In 2004, Pankhurst et al.³⁾ retrospectively

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investigated the history and occurrence rate of malignancies at the time of diagnosis in patients newly diagnosed with AAV and reported that malignancies occurred in 11.5% of microscopic polyangiitis (MPA) cases. MPA is one type of AAV, and it is known to develop after certain circumstances such as infection, drug administration, and malignancy⁶⁾. To gain a better understanding of the coincidence of MPA and malignancy, we retrospectively investigated the occurrence of recent malignancies in MPA patients admitted to the hospital. We determined the concurrence rate of malignancies with MPA and evaluated the clinical characteristics defining MPA cases with malignancies.

Materials and Methods

The subjects included 42 Japanese MPA cases (16 males and 26 females) that were admitted to the St. Marianna University School of Medicine Hospital over a span of 58 months between April 1, 2008 and January 31, 2012. We surveyed all subjects who were admitted to the hospital during this period. In addition to newly developed MPA cases, those who had been previously diagnosed and had disease progression were included in the survey. The diagnosis of MPA was based on the definitions established by the Chapel Hill Consensus Conference¹⁴⁾ or on the diagnostic criteria of the Research Group of Intractable Vasculitis of the Ministry of Health, Labor and Welfare of Japan¹⁵⁾. The control subjects included 126 Japanese cases diagnosed with rheumatoid arthritis (RA) based on the American Rheumatism Association 1987 revised criteria for the classification of RA¹⁶⁾. Control subjects were admitted to the hospital during the same time period and were age- and gender-matched with the MPA group.

“Recently developed malignancies” were defined as all malignancies diagnosed within the two years prior to and including the time of admission. At our hospital, the following examinations were routinely performed for exploration of malignancy in newly hospitalized cases with autoimmune diseases. Screening exams included chest radiograph, chest and abdominal computed tomography (CT), abdominal echography, upper gastrointestinal endoscopy, colonoscopy for patients with a positive fecal occult blood test, colposcopy for female patients, prostate-specific antigen for male patients, and a thyroid echo in the case of struma¹⁷⁾. In addition to these examinations, concurrence of malignancies was diagnosed by pathohistology. In cases of poor general conditions,

not all of the above-mentioned tests could be performed. History of malignancies was determined from medical charts. The rates of recently developed malignancies concurrent with MPA and RA were determined and compared.

Using medical charts, we investigated organ lesions associated with MPA, positive rates of myeloperoxidase (MPO)-ANCA and proteinase-3 (PR-3)-ANCA, and treatment history. Organ lesions in the MPA group were evaluated according to the following methods. Interstitial lung disease (ILD) was evaluated by chest X-rays and high-resolution CT (HRCT), and radiologists diagnosed the disease when they detected interstitial shadows. When abnormal peripheral nerve conductivity was observed in addition to clinical findings of obvious sensory or motor nerve injury, peripheral neuropathy such as mononeuritis multiplex was diagnosed. Glomerular nephritis was diagnosed when urine contained blood and/or an unusually high amount of protein and when urinary sediments showed casts derived from glomeruli. Skin lesions were defined as present when the vasculitis was confirmed pathohistologically and when coupled with obvious vasculitis-derived purpura and ulcers by dermatologists. Arthritis was defined as positive by rheumatologists when joint tenderness and swelling were detected at one or more sites by rheumatologists. Characteristics of organ lesions were compared between MPA cases with and without recently developed malignancies.

This study was approved in advance by the ethics committee at St. Marianna University School of Medicine (approval No. 2527).

Statistical analyses

The statistical analyses were performed using SPSS Statistics, version 22.0 (SPSS Japan Inc., Tokyo, Japan). Age and disease duration are reported as mean $\pm$ standard deviation (SD). Statistical significance was determined using Fisher's exact test, odds ratios [ORs], and 95% confidence intervals [CIs]. P-values of less than 0.05 were considered significant.

Results

Patient characteristics in the MPA group

Table 1 shows the patient characteristics in the MPA group. The group comprised 42 MPA cases (16 males and 26 females) with an average age of 69.9 ± 10.1 years upon admission to the hospital and with average disease duration of 16.0 ± 27.6 months. There were 13 cases with first-onset MPA, 13 that

Table 1. Background of MPA Patients

	MPA (n=42)
Female	61.9%
Age: mean $\pm$ SD (years)	69.9 $\pm$ 10.1
Disease duration: mean $\pm$ SD (months)	16 $\pm$ 27.6
Organ involvement	
Glomerular nephritis	31 (73.8%)
Interstitial lung disease	27 (64.3%)
Arthritis	18 (42.9%)
Peripheral neuropathy	17 (40.5%)
Skin lesions	13 (31.0%)
ANCA positive	
MPO-ANCA	39 (92.9%)
PR3-ANCA	1 (2.4%)

were diagnosed 1–6 months before admission to the hospital, 7 that were diagnosed 7–24 months before hospitalization, and 9 in the chronic stage 25 months or longer before hospitalization.

With regard to organ lesions, glomerular nephritis was most frequently observed (73.8%), followed by ILD (64.3%), arthritis (42.9%), peripheral neuropathy (40.5%), and skin lesions (31%). MPO-ANCA was positive in 92.9% of cases and PR-3 ANCA was positive only in 2.4% of cases.

Characteristics of recently developed MPA cases with malignancies

Table 2 shows characteristics of recently developed MPA cases with malignancies. Concurrent malignancies were observed in eight cases (four males and four females; 19.0%). In cases with malignancies, the average age was 72.9 ± 5.4 years upon admission and the average disease duration of MPA was 10.6 ± 19.1 months. Malignancies included liver cancer in two cases, and one case each of lung cancer, colon cancer, skin basal cell carcinoma, rectal cancer, duodenal cancer, breast cancer, and cervical cancer. Among those, one case developed both breast and

liver cancer. Malignancies were diagnosed two years prior to admission in four cases and upon admission in four cases.

With regard to organ lesions in cases with malignancies, peripheral neuropathy was most frequently observed (75%), followed by ILD (62.5%), skin lesions (50%), and glomerulonephritis and arthritis (37.5% each). When organ lesions were compared between MPA groups with and without malignancies (**Table 3**), the group with malignancies developed peripheral neuropathy more frequently (75% vs. 32.4%; OR, 6.27; 95% CI, 1.09–36.25; $p = 0.045$) and glomerulonephritis less frequently (37.5% vs. 82.4%; OR, 0.13; 95% CI, 0.02–0.69; $p = 0.020$). Skin lesions were observed in 50% of cases, and there was no significant difference between MPA groups with and without malignancies (26.5%; OR, 2.78; 95% CI, 0.57–12.51; p value, 0.236; **Table 3**).

All cases with malignancies were positive for MPO-ANCA. For treatment of recently developed MPA cases with malignancies, corticosteroids were used in 87.5% of cases, and immunosuppressants were employed only in 37.5% (**Table 2**). With regard to surgical treatment of malignancies, all cases that had developed malignancy within the two years prior to the time of admission (Cases 1–4) had already been surgically treated before hospitalization. Meanwhile, only half of the cases that were diagnosed with malignancy upon admission (Cases 5–8) underwent surgery.

Comparison of malignancy rates between control and MPA groups

There were 126 RA cases (48 males and 78 females) in the control group with an average age of 70.1 ± 9.3 years upon admission and average disease duration of 170.6 ± 379.8 months. In the RA group, concurrent malignancies were observed in eight cases (four males and four females; 6.3%) and the average

Table 2. Clinical Characteristics of MPA with Recently Developed Malignancies

No.	Sex	Age (years)	Duration of MPA (months)	Malignant tumor		Organ involvement	ANCA		Therapy
				Type	Time of diagnosis		MPO	PR-3	
1	M	73	0	Liver cancer	<2	ILD, GN	+	-	PSL40 mg
2	F	78	0	Lung cancer	<2	PN, ILD, purpura, livedo reticularis, arthritis	+	-	PSL15 mg
3	M	69	4	Colon cancer	<2	PN, GN, purpura	+	-	PSL45 mg, IVCY
4	F	65	10	Basal cell cancer	<2	ILD, arthritis	+	-	IVCY, AZA
5	M	67	56	Rectal cancer	0	PN, GN, purpura	+	-	m-PSL pulse, IVCY
6	M	77	14	Duodenal cancer	0	PN, ILD, arthritis	+	-	PSL30 mg
7	F	74	0	Breast cancer, Liver cancer	0	PN, ILD, purpura, blisters	+	-	PSL30 mg
8	F	80	1	Cervical cancer	0	PN, skin ulcers, livedo reticularis, hearing	+	-	PSL20 mg

<2: less than two years prior to hospitalization, 0: at the time of hospitalization

PN: Peripheral neuropathy, ILD: Interstitial lung disease, GN: glomerular nephritis

IVCY: intravenous cyclophosphamide pulse therapy, PSL: prednisolone, m-PSL: methylprednisolone pulse therapy, AZA: azathioprine

Table 3. Comparison of Organ Lesions in MPA Cases with and without Malignancies

Organ involvement	MPA [n (%)]		OR (95% CI)		<i>p</i> -value*
	with malignancy (n=8)	without malignancy (n=34)			
Glomerular nephritis	3 (37.5)	28 (82.4)	0.13	0.02-0.69	0.020
Interstitial lung disease	5 (62.5)	22 (64.7)	0.91	0.18-4.48	1.000
Arthritis	3 (37.5)	15 (44.1)	0.76	0.16-3.70	1.000
Peripheral neuropathy	6 (75.0)	11 (32.4)	6.27	1.09-36.25	0.045
Skin lesions	4 (50.0)	9 (26.5)	2.78	0.57-13.51	0.236

**p*-value: Fisher's exact test

age was 71.3 ± 6.4 years. Concurrent malignancies included gastric cancer in two cases and one case each of lung cancer, colon cancer, renal cell carcinoma, prostate cancer, a colorectal carcinoid tumor, and skin basal cell carcinoma. Concurrent malignancies were diagnosed within two years before admission in two cases and on admission in six cases.

Rates of recently developed concurrent malignancies were compared between the MPA (19.0%) and RA groups (6.3%), and the MPA group concurrently developed malignancies significantly more often with an odds ratio of 3.47 (95% CI: 1.21–9.93; *p* = 0.029; Fig. 1).

Discussion

In this study, we investigated the concurrence rate of recently developed malignancies with MPA cases newly admitted to the hospital and evaluated

Figure 1. Comparison of concurrence rates of recently developed malignancies between MPA and RA cases. Odds ratio, 3.47 (95%CI: 1.21–9.93).

**p*-value: Fisher's exact test

the clinical characteristics. Several large-scale studies demonstrated that cases with AAV developed malignancies 1.6–2.4 times as often as the general population^{7–11}. Randomized controlled trials (RCTs) and long-term follow-up (LTFU) studies in Western countries showed that malignancies were observed in 12.6% of MPA cases and 10.8% in cases of granulomatosis with polyangiitis (GPA) during the 87-month follow-up period after treatment for vasculitis^{12)18–21}. Meanwhile, it was suggested that malignancies developed more frequently in vasculitis cases in which immunosuppressants were used to introduce remission and for maintenance therapy. Cyclophosphamide (CYC) has emerged as a major contributor to cancer development because of its direct carcinogenic properties. The most prominent cancers observed in AAV include urinary tract cancer, leukemia, and non-melanoma skin cancer⁶⁾⁷⁾¹³⁾²². Faurschou et al.⁷⁾ reported that malignancies developed at a higher rate two years after the onset of treatment or when the cumulative CYC dose increased (CYC > 36 g) in GPA cases. Most RCTs excluded cases with malignancies that developed before or at the start of the trial. Therefore, the concurrence rates of malignancies before and at the onset of AAV remain poorly understood^{18–21}. In GPA cases, there has been no demonstrated increase of malignancies before the onset to within one year after the onset of vasculitis⁶⁾⁷⁾²³. Pankhurst et al.³⁾ reported in 2004 that concurrent malignancies were observed more frequently before the onset of vasculitis in MPA cases. According to their report, malignancies were concurrently observed in 14 of 122 MPA cases (11.5%). Of those 14 cases, concurrent malignancies occurring within six months after MPA diagnosis were observed in only five cases, while in the nine remaining cases malignancies were observed at least three years prior to MPA diagnosis. In our study, recently developed malignancies were concurrently observed in as many as 9.5% of MPA cases by screening upon admission and in

19.0% of MPA cases when a two-year history was taken into consideration. While direct comparison was difficult due to design differences, our study showed a higher complication rate of malignancy in MPA patients than other studies^{(3)(12)(18–21)}. It is presumed that active malignancy screening had a great impact in this study. Meanwhile, the average age was 69.9 years in MPA cases, a factor that may increase the concurrent rate of malignancies. Moreover, patients that had already received immunosuppressive treatment were included as subjects in this study, and it was impossible to rule out the influence of immunosuppressants on carcinogenesis in the nine MPA patients that had had disease for 25 months or more. We then matched the experimental conditions, including gender and age, and compared the concurrence rate of malignancies between the MPA and RA groups. Immunosuppressants, with methotrexate as the anchor drug, are also used for treatment of RA. In the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) study, a large-scale cohort study on Japanese RA cases, Yamada et al.⁽²⁴⁾ reported that the concurrence rate of malignancies in Japanese RA cases were 1.18-fold higher than that of the general population (SIR1.18, [95% CI, 1.02–1.37]). In our study, MPA cases developed malignancies 3.47 times as frequently as RA cases (**Fig. 1**). Taken together, MPA can be considered an autoimmune disease frequently accompanied by malignancies, and attention should be paid to latent malignancies.

For treatment of MPA patients with malignancy, immunosuppressants are occasionally used and moderate- to high-dose steroids are often administered to the control of vasculitis. Four MPA patients who had developed malignancy within two years before admission did not die within two years after hospitalization. Meanwhile, two patients who were diagnosed with malignancy on admission underwent surgery, and other two patients (50%) died within two years after admission. The cause of death was malignancy-related death. We suspect the reasons for the lower rate of surgical treatment may be cancer progression, delayed wound healing and increased susceptibility to infection by steroids, respiratory and renal dysfunction due to MPA, and increased risk due to old age.

Cancer-associated vasculitis is secondary vasculitis associated with malignancies and accounts for 0.4–4.2% of all vasculitis^(25–27). Cancer-associated vasculitis was categorized into vasculitis associated with probable etiology in the 2012 Revised International

Chapel Hill Consensus Conference⁽²⁸⁾, but an exact definition has yet to be established. In typical cases, hematopoietic malignancies such as myelodysplastic syndromes (MDS) are frequently observed, and vasculitis deteriorates as malignancies advance^{(2)(29–31)}. In addition, skin lesions such as purpura and ulcers were observed in 78.3% of cases and often exhibited leukocytoclastic vasculitis⁽²⁾. On the other hand, in this study, the concurrent malignancies observed were solid cancers, not hematopoietic cancers (**Table 2**). In our cases, none showed an improvement in vasculitis by cancer treatment alone. When characterizing organ lesions, peripheral neuropathy was often observed and glomerulonephritis was less frequently recognized. Skin lesions were observed in half of cases with malignancies. There was no significant difference in the frequency of skin lesions between cases with and without malignancy, though the results may be attributable to the small number of cases. Most cases with cancer-associated vasculitis predominantly developed skin lesions and leukocytoclastic vasculitis was recognized histologically⁽²⁾. Thus, the pathogenesis may be similar to cutaneous leukocytoclastic angitis or cutaneous arteritis. Meanwhile, in this study all MPA cases that recently developed malignancy were positive for MPO-ANCA and showed pauci-immune vasculitis immunohistologically with various organ injuries from AAV. Therefore, it is considered that the etiology, pathogenesis, and clinical manifestations were different between the two groups.

Cancer has been linked with AAV as a potential cause or as a disease-triggering factor⁽²⁾⁽⁶⁾⁽³¹⁾. Though inflammatory responses provoked by the underlying neoplasm contribute to the pathogenesis of vasculitis⁽²⁾⁽⁶⁾⁽²⁹⁾⁽³²⁾, the mechanisms contributing to the development of MPA with malignancies is poorly understood. Further studies are required to clarify the mechanisms underlying the development of malignancy and vasculitis.

Conclusion

In this study, MPA frequently accompanied malignancies of solid cancer. Peripheral neuropathy was observed frequently, but glomerulonephritis less frequently. Because malignancies occurred in up to 20% of MPA cases, those admitted for MPA should be thoroughly screened for malignancies. In Asian countries, no study has investigated complication rates of malignancy in cases with MPA using a large number of cases. Therefore, further study of similar cases is

warranted.

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Conflict of interest: none.

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