Outcomes of melanoma in recipients of solid organ transplant

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Background: There is concern that the immunologic tumor malignant melanoma (MM) may have worse outcomes in immunosuppressed hosts than in the general population.

Objective: We sought to describe outcomes of MM in immunosuppressed solid organ transplant recipients and compare them with the general population.

Methods: We conducted a retrospective review of medical charts and pathology slides of cases of MM and solid organ transplantation between 1978 and 2007, with comparison of outcomes.

Results: In all, 48 MMs were identified in 43 transplant recipients. No patient with MM before transplant receipt had melanoma recurrence, subsequent metastasis, or death caused by melanoma. Of patients with MM diagnosed after transplantation, metastases developed in 3 patients, and two patients died of melanoma.

Limitations: Retrospective review and low number of cases are limitations.

Conclusions: Outcomes of MM in immunosuppressed transplant recipients appeared similar to those in prognostically matched nonimmunosuppressed hosts. The small number of cases limited statistical comparisons. (J Am Acad Dermatol 2008;59:405-17.)

Little is known about the outcomes of malignant melanoma (MM) in immunosuppressed solid organ transplant recipients. Outcomes of MM in nonimmunosuppressed hosts (ie, the general population) have been well documented and vary significantly on the basis of the stage of disease at presentation.[1] Studies have supported a strong influence of the immune system in the pathogenesis and progression of MM.[2-6] Therefore, it would follow that MM could develop more frequently in patients who are immunosuppressed and have worse outcomes.

Abbreviations used:

AJCC: American Joint Committee on Cancer
MM: malignant melanoma
NMSC: nonmelanoma skin cancer

The incidence of MM in transplant recipients is debated, and reports cite a risk of occurrence of 0 to 8 times higher than in the general population.[7,8] The medical literature raises substantial concern regarding poor outcomes in transplant recipients with MM. Unfortunately, these reports lack crucial, complete, and current pathologic staging information, thus limiting their accurate interpretation and application to the management of each case. MM in other subsets of patients who are immunosuppressed, such as patients with HIV or chronic lymphocytic leukemia, is noted to have a potentially more aggressive behavior[9] and increased incidence,[10] respectively. However, the studies reporting these outcomes are small and the mechanism of immunosuppression is different from that in solid organ transplant recipients, making it difficult to

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Table I. Profile of patients with malignant melanoma diagnosed before transplantation*

Patient	Sex	Race	Age at first transplantation, y	Organ transplanted	Reason for transplantation	Induction medications	Maintenance medications	Acute rejection episodes	Chronic rejection	Time from MM to first transplantation, mo	Location of MM	Imaging	AJCC pathologic stage	Treatment of MM	Time from first transplantation to LFU or death, mo	Status at LFU
1†‡	M	W	60	Kidney	Reflux nephropathy	3,4,6,7	3,4,6	. . .	. . .	3	Shoulder	. . .	0	WLE	5	Died of bladder cancer
2§//	M	W	68	Liver	Nonalcoholic steatohepatitis, hepatoma	3,4,6,9	4	. . .	. . .	1	Abdomen	. . .	0	WLE	6	Alive with NED
3	F	W	48	Liver	Autoimmune hepatitis	4,6	4,6	0	. . .	49	Neck	. . .	0	WLE	37	Alive with NED
4	M	W	71	Kidney	Light-chain nephropathy	3,4,8	3,4,6	0	No	43	Cheek	. . .	0	Mohs	38	Died of AML, respiratory insufficiency
5//	F	W	39	Heart	Radiation-induced and ischemic cardiomyopathy	3,4,6	4,5,6	3	No	5	Back	CT	IA	WLE	36	Alive with NED
6¶	M	W	56	Kidney	Uncertain cause	3,4,6	3,4,6	. . .	. . .	78	Chest	MRI, PET	IA	WLE/ SLNB	48	Alive with NED
7//	M	W	52	Liver	Primary sclerosing cholangitis	4,8	4,6	1	No	31	Abdomen	. . .	IA	WLE	188	Alive with NED
8//¶	F	W	47	Kidney	Polycystic kidney disease	3,4,8,9	3,4	1	. . .	41	Abdomen	CT, PET	IB	WLE/ SLNB	25	Alive with NED
9#	M	W	53	Kidney	Polycystic kidney disease	1,8	1,6	0	No	148	Neck	. . .	IB	WLE/ ELND	72	Died of septic shock
10//	M	W	62	Kidney	Nonimmune complex–mediated nephritis	2,3,8	. . .	1	No	155	Forehead	. . .	IV	. . .	24	Died of unknown causes

11	F	W	54	Liver	Alcoholic cirrhosis	1,2,6	2,6	2	No	117	Shoulder	...	Unknown	...	169	Alive with NED
12	M	W	36	Kidney	IgA nephropathy	1,8	1,6	0	No	221	Chest	...	Unknown	...	177	Alive with NED

1, Azathioprine; *2*, cyclosporine; *3*, mycophenolate mofetil; *4*, tacrolimus; *5*, sirolimus; *6*, prednisone; *7*, antilymphocyte globulin; *8*, methylprednisolone; *9*, basiliximab; *AJCC*, American Joint Committee on Cancer; *AML*, acute myeloblastic leukemia; *CT*, computed tomography; *ELND*, elective lymph node dissection; *F*, female; *LFU*, last follow-up; *M*, male; *MM*, malignant melanoma; *MRI*, magnetic resonance imaging; *NED*, no evidence of disease; *PET*, positron emission tomography; *SLNB*, sentinel lymph node biopsy; *W*, white; *WLE*, wide local excision.

*Ellipses indicate not available.

†Patient had an elevated lactate dehydrogenase level and chest radiograph findings negative for cancer.

‡Patient had a second primary MM (in situ) 1 mo after the first (still before transplantation).

§Patient had a second primary MM (in situ) 5 mo after transplantation and, therefore, is also included in Table II.

//Chest radiograph was obtained and findings were negative for cancer.

¶Sentinel lymph node biopsy specimen was obtained and revealed negative findings for cancer.

#Elective lymph node biopsy specimen was obtained and revealed negative findings for cancer.

generalize data from these different immunosuppressed populations.

As the success of solid organ transplantation improves[11] and the survival time after transplantation increases, concern about posttransplantation malignancies is growing.[12] Regardless of a potential increased risk and incidence in transplant recipients, an increased incidence of MM is well documented in the general population.[13-17] The continued increase in MM incidence and the growing solid organ transplantation population at risk for malignancies increase the need to know the natural history, prognosis, and necessary management of this malignancy in the immunosuppressed host.

Three subgroups have been identified for this study, each with its own set of risk factors and management considerations. These subgroups include transplant recipients with a history of MM, recipients with MM diagnosed after transplantation, and recipients who have MM caused by transmission from the organ donor.

This study had two primary objectives: to estimate the MM-specific survival of transplant recipients in whom MM developed after transplantation and to determine the risk of recurrence of MM posttransplantation in recipients who had MM before transplantation on the basis of crucial staging information.

METHODS

The study was approved by the institutional review board at Mayo Clinic. A search of our surgical and medical indices databases of Mayo Clinic, Rochester, Minn, identified patients who had a diagnosis of MM and a solid organ transplantation between 1978 and 2007. Known cases from Mayo Clinic, Scottsdale, Ariz, and Mayo Clinic, Jacksonville, Fla, were also identified. A retrospective chart review was performed, and variables that were abstracted included date of birth, sex, race, Fitzpatrick skin type, family history of MM, personal history of nonmelanoma skin cancer (NMSC), history of dysplastic nevi, history of more than 50 nevi, number of blistering sunburns, number of tanning bed exposures, date of last follow-up, date and cause of death, date of first and any subsequent solid organ transplantations, type of transplant received, disease that led to end organ failure, type of immunosuppressive agents at induction and for maintenance, number of acute rejection episodes, presence of chronic rejection at last follow-up, HLA antigen type, date of diagnosis of MM, location of MM, Breslow thickness, Clark level, ulceration, regression, histiogenic type, radial or vertical growth, mitoses per 10 high-power fields, presence of tumor-infiltrating lymphocytes, neurotropism,

angiolymphatic invasion, associated nevus, sentinel lymph node status, serum lactate dehydrogenase level, elective lymph node dissection status, imaging (ie, chest radiography, positron emission tomography, and computed tomography), 2003 American Joint Committee on Cancer (AJCC) pathologic stage, treatment of MM, presence of recurrence (defined as local recurrence within the scar of the original MM treatment site), presence and date of metastasis, and site of metastasis.

Questionnaires about risk factors were sent to each study-eligible patient or to a family member if the patient was deceased. The questionnaires asked about the following data: sunburn or tanning reaction to sun exposure, hours in the sun at different ages, sunscreen use, personal history of blistering sunburn, number of nevi, presence of dysplastic nevi, family history of MM, personal history of NMSC, use of a tanning bed, and race. In some cases, the data that were obtained from the questionnaire differed from those found in the medical record. The risk factor data were deemed positive if either the medical record or the questionnaire indicated.

One dermatopathologist (R. H. W.) reviewed all obtainable pathology slides (32 [67%] MMs). Because MM staging has changed over the years of the study, all MMs of the patients were assigned, for consistency, a pathologic stage using the 2003 AJCC staging system.

For MMs with a Breslow thickness listed as "at least" a certain number, we evaluated the available re-excision specimens to determine whether residual melanoma was apparent. However, no further melanoma was seen in these cases. These re-excisions were processed in a routine fashion and not with step-sectioning.

Survival by stage of disease was calculated using the Kaplan-Meier method. Outcomes were compared with those reported in the general population.[18] Statistical comparison with significance was not possible because of limited numbers in the study population.

RESULTS

In all, 48 MMs were identified in 43 patients. Thirteen MMs occurred in 12 patients before transplantation, and 34 MMs were found in 31 patients after transplantation. Of these 31 patients, one patient also had an MM before transplantation. Among the 43 patients, one patient was identified whose MM resulted from donor transmission.

Group 1: MM before transplantation

Data for the 12 patients who had MM before transplantation are presented in Table I. The median time between the first MM diagnosis and the organ transplantation was 3.8 years (mean ± SD, 6.2 ± 5.9; range, 0.1-18.4 years). Age at transplantation averaged 53.8 years (±10.6 years; range, 36-71 years). The Breslow thickness ranged from in situ to 2.0 mm, with a median of 0.35 mm. The 2003 AJCC pathologic stages of the 12 patients were 0 (n = 4), IA (n = 3), IB (n = 2), and IV (n = 1); in two patients, the stages were unknown.

No recurrence of MM was identified. In addition, no metastasis was observed after the diagnosis of MM. However, one patient (patient 10) presented initially with a cutaneous metastasis of MM 13 years before transplantation with no primary MM found. This case may have represented a primary dermal melanoma, as proposed by Cassarino et al,[19] because of the excellent survival, but this classification would be difficult to determine. None of the 4 deaths in this group were caused by MM. For the 8 surviving patients, the median time between transplant receipt and last follow-up was 3.5 years (mean ± SD, 7.1 ± 6.5 years; range, 0.5-15.7 years). The 2-year MM-specific survival was 100% for patients in all the represented stages. Therefore, the survival in this population is relatively equivalent to that seen in the general population.[18] Five of the 13 MMs before transplantation were not from Mayo Clinic, Rochester, Minn; one was stage 0, two were stage IA, and two were stage IB.

Group 2: MM diagnosed after transplantation

Data for the 31 patients who had MM diagnosed after transplantation are presented in Table II. The median time between transplantation and MM was 4.7 years (mean ± SD, 5.7 ± 5.4 years; range, 0.2-22.8 years). Age at diagnosis of MM averaged 54.6 years (±12.9 years; range, 28-76 years). Pathology data for both the group with MM before transplantation and for this group with MM diagnosed after transplantation are shown in Table III. In this group, the Breslow thickness ranged from in situ to 6.1 mm (median, 0.75 mm). Tumor-infiltrating lymphocytes were found in 3 patients, in whom there was a nonbrisk inflammatory response. Regression was not observed; an associated nevus was seen in 3 cases. The 2003 AJCC pathologic stages of MM in this group of patients were 0 (n = 8), IA (n = 10), IB (n = 4), IIA (n = 4), IIIA (n = 1), and IIIB (n = 2), and in two patients, the stages were not known.

MM diagnosed after transplantation tended to present at an earlier stage in this case series than in the AJCC cohort[18] (Fig 1). Where available, risk factor data for this group revealed a history of NMSC (18 of 27), a family history of MM (7 of 21), multiple nevi (6 of 18), atypical nevi (11 of 22), tanning bed use (6 of

Table II. Profile of patients with malignant melanoma diagnosed after transplantation*

Patient	Sex	Race	Fitzpatrick skin type	Organ transplanted	Reason for transplantation	Induction medications	Maintenance medications	Acute rejection episodes	Chronic rejection	Time from first transplant to MM, mo	Age at MM, y	Location of MM	Imaging	AJCC pathologic stage	Treatment of MM	Time from first posttransplantation MM to LFU or death, mo	Status at LFU
2†‡	M	W	II	Liver	Nonalcoholic steatohepatitis, hepatoma	3,4,6,10	4	. . .	. . .	6	67	Abdomen	. . .	0	WLE	0	Alive with NED
13	M	W	. . .	Liver	Cryptogenic cirrhosis, nonalcoholic steatohepatitis	3,4,6	5,6	0	No	2	71	Neck	. . .	0	. . .	6	Alive with NED
14	M	W	. . .	Liver	Hepatitis C, hemochromatosis, hepatoma	3,4,6	4	0	No	11	51	Thigh	. . .	0	. . .	13	Alive with NED
15	M	W	II	Kidney	Focal segmental glomerulosclerosis	. . .	3,4,6	. . .	. . .	147	62	Back	. . .	0	WLE	18	Alive with NED
16	M	W	. . .	Liver	Polycystic kidney disease	. . .	2,3,6	0	. . .	67	60	Arm	. . .	0	WLE	47	Alive with NED
17	F	W	. . .	Liver	Primary biliary cirrhosis	3,4,6	3,4,6; then 4	0	. . .	28	49	Forearm	. . .	0	WLE	59	Alive with NED
18‡	M	W	II	Kidney	. . .	. . .	2,3,6	. . .	. . .	46	56	Wrist/ hand	. . .	0	WLE	62	Alive with NED
19‡	F	W	III	Kidney	Ureteropelvic kidney disease	1,8	1,6	0	No	99	29	Back	. . .	0	WLE	284	Alive with NED
20	M	W	. . .	Liver	Nonalcoholic steatohepatitis	3,4,6	3,4; then 2,3; then 5,6	0	. . .	15	59	Back	. . .	IA	. . .	6	Alive with NED
21	M	W	. . .	Liver	Primary sclerosing cholangitis	3,4,6	3,4,6	1	Yes	3	35	Back	. . .	IA	. . .	7	Alive with NED

Continued

Table II. Cont'd

Patient	Sex	Race	Fitzpatrick skin type	Organ transplanted	Reason for transplantation	Induction medications	Maintenance medications	Acute rejection episodes	Chronic rejection	Time from first transplant to MM, mo	Age at MM, y	Location of MM	Imaging	AJCC pathologic stage	Treatment of MM	Time from first posttransplantation MM to LFU or death, mo	Status at LFU
22[‡]	M	W	III	Liver	Hepatitis C, alcoholism	3,4,6	4	0	No	4	48	Abdomen	. . .	IA	WLE	9	Died of unknown causes
23	M	W	II	Liver	Chronic renal insufficiency, uncertain cause	3,4,6	3,4,6; then 2,3,6; then 5,6	. . .	Yes	8	71	Nose	. . .	At least IA	. . .	11	Alive with NED
24[‡§]	M	W	III	Liver	Nonalcoholic steatohepatitis, cirrhosis	3,4,6	4	0	No	9	58	Abdomen	. . .	IA	WLE	42	Alive with NED
25[‡//]	F	W	II	Kidney/ pancreas	Diabetic nephropathy	1,2,8	1,2,6	1	. . .	101	53	Nose	. . .	At least IA	Mohs	54	Alive with NED
26[‡¶]	M	W	II	Liver	Hepatitis C, alcoholism	3,4,6	3,4	0	No	14	70	Back	CT	IA	WLE	63	Alive with NED
27[‡]	F	W	IV	Lung	Lymphangioleiomyomatosis	. . .	2,6	0	No	111	45	Thigh	. . .	IA	WLE	70	Alive with NED
28	F	W	II	Kidney	. . .	. . .	3,4,6 (3,4,6)[#]	1	. . .	162	28	Foot	. . .	IA	. . .	83	Alive with NED
29[‡]	F	W	III	Liver	Primary sclerosing cholangitis	1,2,8	1,4,6	1	No	58	52	Thigh	. . .	IA	WLE	109	Alive with NED
30[‡]	M	W	II	Heart	Idiopathic dilated cardiomyopathy	1,2,9	1,2,6	4	No	97	76	Back	. . .	IB	WLE	4	Died of myocardial infarction
31[‡**††]	M	W	II	Kidney	Hypertension and light-chain nephropathy	. . .	. . .	. . .	Yes	273	68	Shoulder	. . .	IB	WLE/ SLNB	17	Died of metastatic lung SCC
32[**‡‡]	M	W	. . .	Heart	Amyloidosis	. . .	1,2,6	0	No	81	63	Neck	CT, PET	IB	WLE/ SLNB	21	Died of MM

33[‡]	M	W	. . .	Kidney	Focal sclerosing glomerulonephritis	1,2,6	1,2,6	1	No	24	55	Arm	. . .	IB	WLE	144	Died of unknown causes
34[‡]	M	W	II	Heart	Dilated cardiomyopathy	. . .	. . .	0	No	149	55	Scalp	. . .	IIA	WLE	1	Alive with MM
35[‡]	M	W	IV	Kidney	Hypertensive nephrosclerosis	1,2,8 (1,2,6,7)[#]	1,2,6 (1,4,6)[#]	1	Yes	118	76	Neck	CT	At least IIA	WLE	1	Died of renal failure
36[‡**††]	M	W	III	Kidney	Glomerulonephritis	3,4,6	2,3,6	0	Yes	12	40	Leg	CT, PET	IIA	WLE/ SLNB	42	Alive with NED
37[‡§§]	F	W	. . .	Kidney	Diabetic nephropathy	1,2,8	1,2,6	0	No	87	32	Shoulder	. . .	IIA	WLE	84	Died of MM
38[‡////]	F	W	. . .	Kidney	Diabetes mellitus	. . .	4,6	0	No	30	53	Back	CT, PET	IIIA	WLE/ SLNB	37	Alive with NED
39[////]	F	W	. . .	Heart	Dilated cardiomyopathy	. . .	1,2	3	No	168	59	Leg	PET	IIIB	WLE/ SLNB	12	Alive with NED
40[¶¶]	M	W	III	Kidney	Diabetic nephropathy	. . .	1,2,6	0	No	31	55	Scalp	. . .	IIIB	WLE	105	Died of unknown causes
41	F	W	II	Kidney/ pancreas	Diabetes mellitus	1,2,6	1,2,6	1	Yes	95	44	Scalp	. . .	Unknown	. . .	91	Alive with NED
42	F	W	. . .	Kidney	Primary hyperoxaluria	. . .	. . .	. . .	Yes	56	53	Nose	. . .	Unknown	. . .	104	Alive, MM status unknown

1, Azathioprine; *2*, cyclosporine; *3*, mycophenolate mofetil; *4*, tacrolimus; *5*, sirolimus; *6*, prednisone; *7*, antilymphocyte globulin; *8*, methylprednisolone; *9*, hydrocortisone; *10*, basiliximab; *AJCC*, 2003 American Joint Committee on Cancer; *CT*, computed tomography; *F*, female; *LFU*, last follow-up; *M*, male; *MM*, malignant melanoma; *NED*, no evidence of disease; *PET*, positron emission tomography; *SCC*, squamous cell carcinoma; *SLNB*, sentinel lymph node biopsy; *W*, white; *WLE*, wide local excision.

*Ellipses indicate not available.

[†]Patient 2 had his first of two primary MM (in situ) 1 mo before transplantation and, therefore, is also included in Table I.

[‡]Chest radiograph was obtained and findings were negative for cancer.

[§]Lactate dehydrogenase level was elevated.

[//]Patient 25 had a recurrence on the nose at age 55 y (26 mo after the primary MM); the MM had a Breslow thickness of 1.05 mm and was treated with WLE and SLNB (negative).

[¶]Patient 26 had a second primary MM on the temple at age 75 y (61 mo after the first primary MM and 75 mo after receiving the transplant); the MM had a Breslow thickness of 0.75 mm and was treated with Mohs micrographic surgery.

[#]Parentheses indicate second transplantation.

**Sentinel lymph node biopsy sample was obtained and revealed negative findings.

[††]Lactate dehydrogenase level was normal.

[‡‡]Patient 32 at age 64 y had a recurrence on the neck (10 mo after the primary MM), a second primary MM (in situ) on the arm (99 mo after receiving the transplant), and metastases to the lung (12 mo after the first primary MM). He died of MM 9 mo later at age 65 y.

[§§]Patient 37 had a metastasis to pleura at age 36 y (49 mo after the primary MM). She died of MM at age 39 y (35 mo after metastases were diagnosed).

[////]Sentinel lymph node biopsy sample was obtained and revealed positive findings.

[¶¶]Patient 40 presented with satellite metastases (stage IIIB) and had a second primary MM on the back at age 57 y. This MM was nodular and had a Breslow thickness of 1.7 mm and Clark level IV and was treated with WLE and SLNB (status unknown). He had metastases to lung and bone 19 mo later and died 7 mo afterward of unknown causes at age 59 y.

Table III. Pathology data for malignant melanoma before transplantation and malignant melanoma diagnosed after transplantation[*†]

Patient	Pathology reviewed	Breslow thickness, mm	Clark level	Ulceration	Histiogenic type	Radial growth phase	Vertical growth phase	Type of vertical growth	Mitoses/ 10 HPF	Regression
1	Y	IS	I	N	SS	Y	N	N/A	N/A	N/A
1[‡]	Y	IS	I	N	LM	Y	N	N/A	N/A	N/A
2	Y	IS	I	N	SS	Y	N	N/A	N/A	N/A
2[‡]	Y	IS	I	N	SS	Y	N	N/A	N/A	N/A
3	Y	IS	I	N	LM	Y	N	N/A	N/A	N/A
4	N	IS	I	...	...	Y	N	N/A	N/A	N/A
5	Y	0.40	II	N	SS	Y	N	N/A	N/A	N/A
6	N	0.96	IV	...	...	...	Y	...	...	...
7	Y	0.35	II	N	SS	Y	N	N/A	N/A	N/A
8	N	1.30	...	...	...	...	Y	...	...	...
9	N	2.00	...	...	...	...	Y	...	...	...
10	N	...	...	...	...	...	...	...	...	...
11	N	...	...	...	...	...	...	...	...	...
12	N	...	...	...	...	...	...	...	...	...
13	Y	IS	I	N	SS	Y	N	N/A	N/A	N/A
14	Y	IS	I	N	SS	Y	N	N/A	N/A	N/A
15[§]	Y	IS	I	N	SS	Y	N	N/A	N/A	N/A
16	Y	IS	I	N	LM	Y	N	N/A	N/A	N/A
17	Y	IS	I	N	SS	Y	N	N/A	N/A	N/A
18	Y	IS	I	N	SS	Y	N	N/A	N/A	N/A
19[§]	N	IS	I	...	SS	Y	N	N/A	N/A	N/A
20	Y	0.83	II	N	SS	Y	N	N/A	N/A	N/A
21	Y	0.30	II	N	SS	Y	N	...	...	...
22	Y	0.52	II	N	SS	Y	N	...	...	...
23	Y	At least 0.75	At least II	N	LM	Y	N	N/A	N/A	N/A
24[¶]	Y	0.52	III	N	SS	Y	Y	Spindle	0	N
25	Y	At least 0.50	At least II	N	SS	Y	Y	Epithelioid	1	N
25[//]	N	1.05	...	...	...	Y	Y	...	...	...
26	Y	0.32	II	N	SS	Y	N	N/A	N/A	N/A
26[‡]	N	0.75	...	...	LM	Y	...	...	...	...
27	Y	0.38	II	N	SS	Y	N	N/A	N/A	N/A
28	N	0.80	...	...	...	...	...	...	...	...
29[§]	Y	0.35	II	N	SS	Y	N	N/A	N/A	N/A
30[¶]	Y	1.20	IV	N	Nodular	N	Y	Epithelioid	2	N
31	Y	1.08	III	N	SS	Y	Y	Epithelioid/ spindle	2	N
32	N	2.00	...	...	...	...	...	...	...	...
32[//]	N	...	...	...	...	...	...	...	...	...
32[‡]	Y	IS	I	N	SS	Y	N	N/A	N/A	N/A
33	Y	1.01	IV	N	SS	Y	Y	Epithelioid	3	N
34	Y	2.75	V	N	Desmoplastic	N	Y	Spindle	1	N
35	Y	At least 2.50	At least IV	N	SS	Y	Y	Epithelioid	5	N
36	Y	2.75	IV	N	SS	Y	Y	Epithelioid	2	N
37[¶]	Y	2.90	IV	N	Nodular	N	Y	Epithelioid	5	N
38	Y	6.10	IV	N	Nodular	Y	Y	Epithelioid	3	N
39	Y	1.90	IV	Y	SS	Y	Y	Epithelioid	7	N
40	N	2.30	IV	...	...	...	Y	...	...	...
40[‡¶#]	N	1.70	IV	...	Nodular	N	Y	...	7	...
41	N	...	...	...	...	...	...	...	...	...
42	N	...	...	...	...	...	...	...	...	...

HPF, High-power field; *IS*, in situ; *LM*, lentigo maligna; *N*, no; *N/A*, not applicable; *SS*, superficial spreading; *Y*, yes.

*Ellipses indicate not available.

[†]No neurotropism or angiolymphatic invasion was seen in the cases reviewed.

[‡]Patient had pathology data for a subsequent primary malignant melanoma.

[§]Associated nevus was seen and was compound.

[¶]Tumor-infiltrating lymphocytes were seen but inflammatory response was nonbrisk.

[//]Patient had pathology data for a local malignant melanoma recurrence.

[#]Microsatellites were seen.

16), and a history of blistering sunburns (10 of 16). Among the risk factor data responses, 67% were completed by the patient; the remainder were completed by a family member.

Patient 32, who had stage IB MM, and patient 25, who had stage IA, experienced a recurrence of MM at 0.8 and 2.2 years, respectively. Patient 32 also had lung metastasis at 1 year after diagnosis of MM. In addition, patient 37, who had stage IIA, had metastasis to the pleura at 4.1 years after diagnosis of MM, and patient 40, who had stage IIIB, had metastasis to lung and bone at 2.9 years after diagnosis of MM.

Eight patients died of any cause (median time to death, 1.6 years; range, 0.1-12 years). The Kaplan-Meier survival estimates for death as a result of any cause were 89.3%, 80.1%, and 80.1% at 1, 3, and 5 years, respectively. Two of these patients died because of MM at 1.8 years and 7.1 years after the primary diagnosis. For the 23 patients who were alive at last follow-up, the median duration between MM diagnosis and last follow-up was 3.6 years (mean ± SD, 4.4 ± 5.1 years; range, 0-23.7 years). Given that only one of the 31 patients died within 2 years, the survival could indicate a trend relatively equivalent to that seen in the general population[18] (Table IV). Eleven of 34 MMs after transplantation were not from Mayo Clinic, Rochester, Minn. These 11 MMs occurred in 9 patients; 5 were in situ and 6 were stage IA.

Group 3: MM caused by donor transmission

One transplant recipient had donor-transmitted MM. A few months after the living, related donor gave his kidney for transplantation, he received a diagnosis of MM metastatic to the brain and died of his disease. After discussion of allograft removal because of the risk of transmission versus observation, the recipient elected to maintain the allograft and be observed in follow-up. One year later, metastatic MM was detected in the recipient. Immunosuppression was discontinued, and the allograft, spleen, grafted kidney, and portions of liver and mesentery were removed. Eleven years later, at last follow-up and without retransplantation, the patient was alive with no evidence of MM.

DISCUSSION

This study presents the most complete data of staging and outcomes currently reported for a case series of MM in transplant recipients. Although it does not statistically confirm or refute a worse prognosis of MM in solid organ transplant recipients, its trends differ from those of previous case reports and case series published in the medical literature, which had raised concern for a worse prognosis.

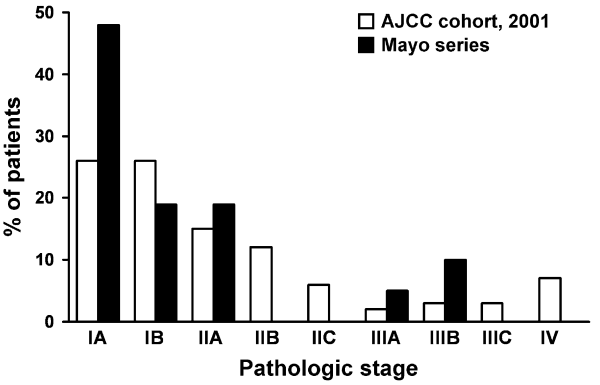

Fig 1. Pathologic stage at presentation of de novo malignant melanoma after transplantation. *AJCC*, American Joint Committee on Cancer.

Specifically, in the group with MM before transplantation, we identified no recurrences, metastases after transplantation, or death caused by MM among the 12 patients in this group. These results differ from the findings of one previously published series, in which transplant recipients with a history of MM before transplantation were reported to have a high incidence of recurrence of MM after transplantation, with poor outcomes.[20] In this previous study of 31 patients with MM that was diagnosed and removed at a median of 25 months before transplantation, 6 patients (19%) had MM recurrence after transplantation. All of these 6 patients died of their recurrent MM at a mean of 16 months after its diagnosis, with an average follow-up period of 32 months for the series.

Although the number of cases in this previous report is greater than in the current study, staging information was lacking in the previous report. Only one MM was known to be Clark level IV, with Breslow thickness unknown. Interpretation of the recurrence and mortality in this prior study is, therefore, difficult without knowing more prognostic information. If the tumors were deep or of an advanced stage, recurrence and death would not be surprising, regardless of whether the patient had been receiving immunosuppressive agents for a transplanted organ. In comparing this study by Penn[20] with the current study, one must take into account that patients in the prior study may have had fewer regulations for transplantation qualification, and, therefore, patients who received transplants may have had a history of higher-risk MM than patients in the current series. It is not possible to confirm this idea, but it must be taken into account.

In the group with MM diagnosed after transplantation, 8 of the 31 patients were known to have died of any cause at last follow-up, but only two of the 31 patients died of melanoma. There were two patients with recurrences (stages IA and IB) and 3 patients with metastasis (stages IB, IIA, and IIIB). Most of the

Table IV. Survival based on 2003 American Joint Committee on Cancer pathologic stage

AJCC pathologic stage	MM, no.	Mayo series: Median follow-up after MM (individual follow-up/patient), y[†]	AJCC cohort*: 2-y MM-specific survival, %
In situ	8	2.7 (0, 0.5, 1.1, 1.5, 3.9, 4.9, 5.2, 23.7)	N/A
IA	10	4.0 (0.5, 0.6, 0.8, 0.9, 3.5, 4.5, 5.3, 5.9, 6.9, 9.1)	99.0 ± 0.2
IB	4	1.6 (0.3, 1.5, 1.8 [died], 12)	97.3 ± 0.3-98.7 ± 0.3
IIA	4	1.8 (0.1, 0.1, 3.5, 7.1)	92.9 ± 0.9-94.3 ± 0.6
IIIA	1	3.1	82.7 ± 3.8-88.0 ± 2.3
IIIB	2	4.9 (1.0, 8.8)	65.6 ± 5.0-81.0 ± 4.1
Unknown	2	8.1 (7.6, 8.7)	...[‡]

AJCC, 2003 American Joint Committee on Cancer; *MM*, malignant melanoma; *N/A*, not reported.
*Data from Balch et al,[1] presented as range of reported Kaplan-Meier survival estimates ± SE.
[†]All patients were alive at last follow-up unless indicated otherwise.
[‡]Ellipsis indicates not available.

MMs were not advanced. To summarize, among the MMs of stages 0 to IB, one patient (with stage IB) of the 22 patients experienced a recurrence, had metastases, and died of MM. In addition, one patient (with stage IA) had a recurrence after 26 months but was alive without disease after an additional 28 months. Of the 7 patients with stage IIA or greater, two patients had metastases (stages IIA and IIIB) and one of them died of MM (stage IIA).

Again, data regarding outcomes of MM diagnosed after transplantation are sparse in the medical literature. Only 4 studies provide any prognostic information with outcomes.[8,20-22] In a large series of 177 transplant recipients in whom de novo MM developed, 56 died of MM.[20] Breslow thickness ranges with cutoffs at 0.75, 1.50, and 4.0 mm were known for 42 patients, including only 14 (25%) of the 56 who died of MM. Twelve of 29 patients whose MM had a Breslow thickness greater than 0.76 mm died of melanoma. It is interesting to note that two patients who had MM with a Breslow thickness less than 0.76 mm died of MM. No other study with staging information reports death caused by MM less than or equal to 1 mm in an immunosuppressed transplant recipient.[8,20-22]

When evaluating characteristics of MM diagnosed after transplantation for insight into potential pathogenesis, previous studies have asserted that MMs may behave more aggressively because the immune system of a patient who is immunosuppressed is not responsive to keeping the MMs in check. Specifically, Greene et al[22] found a paucity of "lymphocyte/macrophage infiltrate" in these MMs compared with the infiltrate amount expected in the general population with MM. However, their criterion for this infiltrate appears to be different from that used in our study. For our purposes, tumor-infiltrating lymphocytes were defined as lymphocytes in the main body of the MM, as opposed to solely surrounding the tumor. These lymphocytes were subclassified as brisk or nonbrisk on the basis of the degree of inflammation. In addition, this feature is only applicable in MMs that have a vertical growth phase. Because true tumor-infiltrating lymphocytes and macrophages seem to be relatively infrequent in the general population,[2] it was not surprising that, in our study, most MMs did not have this feature, and when the feature was present, the response was nonbrisk. Previous medical literature has also claimed that a nevus is a common finding in MMs in immunosuppressed transplant recipients and that, because the immune response is suppressed, atypical nevi are not kept in check but are allowed to progress into melanoma.[22] We found 3 MMs (of 28 MMs) in this immunosuppressed group for which we have data of an associated nevus, none of which were histologically atypical (Clark's) nevi. In this study, we are not intending to imply, or to address the debate, that atypical nevi are precursors to MM; this observation is simply in follow-up to previous reports.

MM is reported to be an immunologic tumor.[2-6] There is a central role for T lymphocytes in effective host immune responses against cancer.[23,24] Many melanoma vaccines are designed to use dendritic cells to present antigen and initiate the T-cell response through both naïve and memory $CD8^+$ and $CD4^+$ T lymphocytes. Attempts to use interleukin 2 to stimulate an immune response have shown some promise,[25] and other studies have shown that patients with advanced cancer produce less T_H1 cytokines in response to stimulation than do healthy control subjects.[6] Immunosuppressive medications used in solid organ transplant recipients have a primary focus of inhibiting T-cell activation. Some immunosuppressive medications, such as tacrolimus, may inhibit T-cell activation by preventing dephosphorylation and translocation of nuclear factor of activated T cells, a nuclear component thought

to initiate gene transcription for the formation of such lymphokines as interleukin 2 and interferon-γ.

Exact mechanisms of immunosuppression for many transplant regimens are not known, making it difficult to determine a common or causative link with the potential role of immunosuppression in solid organ transplant recipients with MM. Another consideration is the tumorigenic effects of the immunosuppressive medications given to solid organ transplant recipients. For example, cyclosporine is known to interfere with DNA repair mechanisms, and, in general, calcineurin inhibitors may promote cancer cell invasiveness and progression by transforming growth factor-β—driven mechanisms.[26-29]

It is notable that in our series, patients who had MM diagnosed after transplantation presented, on average, at a less advanced stage than those in the AJCC cohort. Of 29 de novo MMs for which stage was known, 8 were in situ. A more advanced stage at presentation could be expected because of immunosuppression in solid organ transplant recipients, if this immunosuppression truly did allow the MM to progress in a more aggressive fashion. Conversely, MM may be diagnosed at an earlier stage in transplant recipients because this population is observed so closely by the medical profession. Transplant recipients at this study institution specifically are observed closely in a multidisciplinary transplant center that includes a very active dermatology clinic.

Risk factors for MM in this study population appeared similar to those in the general population. Of the patients for whom we had data, nearly two-thirds had a history of NMSC or of blistering sunburns; half had a history of histologically atypical nevi; approximately one-third had a history of multiple nevi or of tanning bed use; and one-fourth had a family history of MM. Of these risk factors, a history of NMSC and a family history of MM appear to be overrepresented. The expected rate of a family history of MM in persons in the general population who have MM is only 8% to 10%.[30,31] Patients with a history of NMSC have a relative risk of 3 to 17 for development of a subsequent MM.[32] With the increasing incidence of NMSC in the general population and the known increased risk of these cancers in transplant recipients, it is understandable that many transplant recipients with MM have a history of NMSC.

Organ donors with a history of MM have been identified as persons who present significant risk of melanoma transmission to prospective transplant recipients. Cases of metastatic MM transmitted with the donated organs leading to high mortality in the recipients[20-36] have been reported. Penn[33] recorded data of 13 donors with MM who provided organs to 28 recipients. Melanoma was transferred to 21 (75%) recipients, and 13 (62%) of the 21 died of the disease. Other case reports have shown a 50%[37] to 100%[34,38] transmission and mortality.

It has been previously reported that no patient with invasive melanoma should ever be an organ donor.[36] In our experience, we found only one case of donor-transmitted MM, and, despite widespread metastases in the recipient, the outcome was favorable. However, this is only one anecdotal case.

Limitations

The most notable limitation in this study is the number of patients and of cases of MM, which is too small to allow meaningful statistical analysis and valid statistical comparisons. In addition, the limited number of events (death caused by disease) prevented evaluation of the effect of risk factors and various prognostic factors on outcomes. Specifically, in an attempt to determine outcomes on the basis of the stage of disease within each clinical scenario, which needs to be done to answer clinical questions, numbers were very small.

Any retrospective case series has inherent limitations, as does a study involving a questionnaire sent to patients or to family members of deceased patients. Our risk factor data are not robust because of recall bias on the part of the patient and the patient's family members[39]; however, the data can serve as a point of interest to be built on in future prospective studies. Although the MM of most of our patients could be staged on the basis of the data available, our data are unfortunately incomplete for some study variables.

Our capture of all cases of MM in patients with transplantation within the 3 sites of Mayo Clinic also may not be complete. Although we were able to use comprehensive databases at Mayo Clinic, Rochester, Minn, we were not able to do this at Mayo Clinic, Jacksonville, Fla, and Mayo Clinic, Scottsdale, Ariz, because they do not have an established comprehensive database, thereby adding a potential element of selection bias. Of specific concern, those cases known by recall could be of a more advanced stage. However, when Mayo Clinic, Rochester, Minn, cases are compared with those of Mayo Clinic, Jacksonville, Fla, and Scottsdale, Ariz, the non—Rochester, Minn, cases are actually of an early stage. The true impact of any recall bias for non—Rochester, Minn, cases is difficult to assess, because 16 of the 43 cases of MM were non—Rochester, Minn, cases and the removal of these cases would cut the total number nearly in half. At a tertiary care center such as Mayo Clinic, there is always potential for referral bias. Despite the fact that we tried to make the questionnaires objective and

reliable, they were not validated questionnaires and were subject to interpretation and recall bias by the persons completing the forms.

Several features of the patients in our series also limit the generalizability of our results. Our results may be biased as a result of the close dermatologic monitoring encouraged at our institution for patients with transplantation. Most of our patients presented at a relatively early stage, so we cannot shed much light on the behavior of more advanced MM in these groups. In addition, all patients were white, a fact that limits applicability to other races. The patients in this series had received various transplant organ types and were treated with varying immunosuppression regimens with likely different degrees of immunosuppression, which also limits the ability to generalize outcomes to all patients with transplantation.

Conclusion

Physicians are often called on to advise about the appropriateness of solid organ transplantation for a potential recipient with a history of MM pretransplantation, the appropriateness of allowing transplantation of a solid organ from a donor with a history of MM, and the prognosis and proper treatment of immunosuppressed transplant recipients in whom MM develops after transplantation. Previously described voids in the current literature regarding outcomes in these situations make them difficult to manage in an evidence-based fashion.

According to this small retrospective case series, outcomes of MM in immunosuppressed transplant recipients appear similar to those in prognostically matched nonimmunosuppressed hosts. Concern does exist that immunosuppressed transplant recipients with MM with a pathologic stage greater than IIA may have poor outcomes with significant risk of metastasis, but the number of cases in this study is too low to allow comparison with the general population. Further study that evaluates larger patient populations is needed to attain statistically significant comparisons, especially as determined by specific stage of disease.

With the current level of evidence that pertains to all 3 patient groups of interest, evidence-based decision making is limited. Until larger studies are performed, management must be done case by case, with professional judgment based on knowledge of MM in the general population and caution with consideration of the outcomes of the case reports and case series of MM in transplant recipients.

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