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"Syndrome myxoma": a subset of patients with cardiac myxoma associated with pigmented skin lesions and peripheral and endocrine neoplasms

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SUMMARY From January 1954 to December 1985 cardiac myxoma was diagnosed in 75 patients at the Mayo Clinic. The clinical presentation was typical in 70 cases and was referred to as "sporadic myxoma". Forty four other cases of cardiac myxomas (five from the Mayo Clinic) presented with a combination of distinctive clinical features and these cases are described as "syndrome myxoma". The patients with syndrome myxoma were younger (mean age, 25 *vs* 56 years) and had unusual skin freckling (68%), associated benign non-cardiac myxomatous tumours (57%), endocrine neoplasms (30%), and a high frequency of familial cardiac myxoma (25%) and familial endocrine tumours (14%). The two types of cardiac tumour were different (syndrome *vs* sporadic): atrial location, 87% *vs* 100%; ventricular location, 13% *vs* 0%; single tumour, 50% *vs* 99%; multiple tumours, 50% *vs* 1%; and recurrent tumour, 18% *vs* 0%.

It is concluded that patients with syndrome myxoma represent a distinctive subgroup in which there are important clinical, surgical, and genetic implications. More importantly, syndrome myxoma appears to be only one expression of a much larger disease entity.

Although it is rare, cardiac myxoma is the most frequently encountered primary neoplasm of the heart.[1] Cardiac myxomas are typically sporadic, benign, non-recurring, left atrial tumours.[1] They are usually attached to the atrial septum, in or about the valve of the fossa ovalis, and are more common in females and in patients aged from 30 to 60.[2]

From a review of experience at the Mayo Clinic and a critical review of published reports we recognised a subset of patients with cardiac myxoma and associated systemic manifestations including pigmented skin lesions and non-cardiac tumours.[3] These patients have distinctive clinical features that separate them from the larger group of patients with the more common sporadic myxoma.[2] We call the condition in this subset of patients "syndrome myxoma".

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We have compared sporadic myxoma with syndrome myxoma and we summarise the specific findings that allow clinical distinction between the two. The most important distinction is that syndrome myxoma appears to be a multisystem disease.

Patients and methods

From 1954 to 1985, 75 patients with cardiac myxoma were seen at the Mayo Clinic. Seventy of them had the sporadic type of cardiac myxoma. Five (7%) patients have subsequently been recognised as having an atypical presentation and these were the original cases that prompted the use of the term syndrome myxoma. We defined syndrome myxoma as cardiac myxoma with one or more of the following features: cutaneous lentiginosis or unusual hyperpigmented skin lesions (that is, unusual or excessive freckling), non-cardiac myxoid tumours or neurofibromas, or a rare endocrine neoplasm. When we used these three criteria to review published reports we found 39 additional cases of syndrome

Table 1 *Details of 44 patients with syndrome myxoma*

Case No	*Reference*	*Age (yr)*	*Sex*	*Cardiac myxoma*	*Pigmented macules*	*Non-cardiac myxoma*	*Other*	*Familial feature*	*Clinical features*
1	4	16	M	LA and LV (S)	+	—	—	–	Blue naevi (multiple)
2	5	10	M	Biatrial (S)	+	Sk (NF)	AH	–	Blue naevi
3	6	29	M	LA and RV (S)	–	Sk	—	–	Hürthle cell thyroid adenoma
4	7	26	F	4 in RA (S)	–	Sk, Br, U	AH, pheo	+	Sister of case 5
5	7	?	F	Site unknown	+	Sk, Br	AH	+	
6	8	16	M	RV	–	Sk	LCCSC	–	
7	9	12	F	RA	–	Br	AH	+	Mother had LA myxor
8	10	29	F	Biatrial (S)	+	—	—	–	
9	11	22	F	Biatrial (S)	+	—	—	–	
10	12	16	F	LA	+	Sk, Br	—	+	Four myxoma operations
		18		LA (R) (multiple)					(see fig 3)
		20		RA and LA (R) (multiple)					
		29		RA (R)					
11	12	56	M	LA	+	Sk	—	+	Father of case 10 (see fig 3)
12	13	14	F	Biatrial (S)	+	—	—	–	
13	14	45	F	RA, LA, RV, LV (S)	–	Sk	AH	–	
14	15	46	M	LA (2 stalks)	–	Sk	—	+	Possible acromegaly
		46		4 LA					
		52		6 LA					
				RA					
15	16	23	M	RV	–	Sk	LCCSC	+	Identical twin with RV myxoma
16	17	?	F	Site unknown	–	—	AH	–	
17	18	12	F	2 LA (S)	+	—	—	–	Hispanic
18	19	25	F	RA		Sk, Br	—	+	
19	20	24	F	LA, LV (S)	+	Sk, Br	—	+	Brother with acromegaly, cardiac myxoma, lentigines
20	21	18	M	LA	–	Sk	—	–	3 myxoma operations
21	22	19	M	RA	+	—	—	–	
22	23	14	M	LA	+	—	—	–	
23	24	26	M	RV	+	—	Test. tumour	–	
24	25	16	M	LV	+	—	AH, LCCSC	+	Brother of case 25
25	25	10	M	LA	+	—	AH, LCCSC	+	Brother of case 24
26	26	?	F	Site unknown		—	Acromegaly	–	
27	27	18	M	LA	+	Palate NF	—		2 myxoma operations
		?	M	LV (R)					
28	28	10	F	RA	+	Sk, Br, vulva	—	–	Blue naevi
29	28	?	F	Site unknown	+	—	—	+	
30	28	?	M	Site unknown	+	—	—	+	
31	28	?	F	Site unknown	+	—	—	+	
32	29	33	F	LA	–	Br, FA	—	–	2 myxoma operations
	30	39		LA (R)					
33	29	37	F	LA	–	Br, FA	—	–	
34	31	36	F	LA	+	Br, FA, Sk	AH	+	Brother with LA myxoma
35	32	25	F	RA, 2 LA (S)	–	Palate NF	—	+	Hispanic, sister with LA myxoma
36	33	30	F	RV	+	Br, vulva, NF	—	–	
37	34	15	F	RA, 2 LA (S)	+	Sk	—	–	
38	PC	12	F	Biatrial (S)	+	—	—	–	Hispanic
39	PC	37	F	LV	+	—	—	–	Multiple naevi
40	Mayo	17	F	Biatrial (S)	+	Sk	—	–	2 myxoma operations
		19		RA (R)		Sk	—		
41	Mayo	32	F	3 RA (S)	+	Br, FA	—	–	3 myxoma operations (see fig 4)
		35		4 LA (S)					
		45		LA (R)					
42	Mayo	33	F	LA	+	—	—		
43	Mayo	52	M	LA	+	Vocal cord	—	–	
44	Mayo	33	F	RA	+	Sk	—	–	2 myxoma operations
		43		2 RA, LA (R) (S)					

AH, adrenal hyperplasia; Br, breast; FA, fibroadenoma; LA, left atrium; LCCSC, large cell calcifying Sertoli cell testicular tumour; LV, left ventricle; NF, neurofibroma; PC, personal communication; pheo, pheochromocytoma; R, recurrence; RA, right atrium; RV, right ventricle; S, synchronous; Sk, skin; Test., testicular; U, uterus; V, ventricle; ?, not known.

myxoma. Each example was originally reported as an isolated case. We compared the 44 cases of syndrome myxoma with the 70 cases of sporadic cardiac myxoma at the Mayo Clinic.

Results

SYNDROME MYXOMA PATIENTS

Table 1 shows data on the 44 patients with syndrome

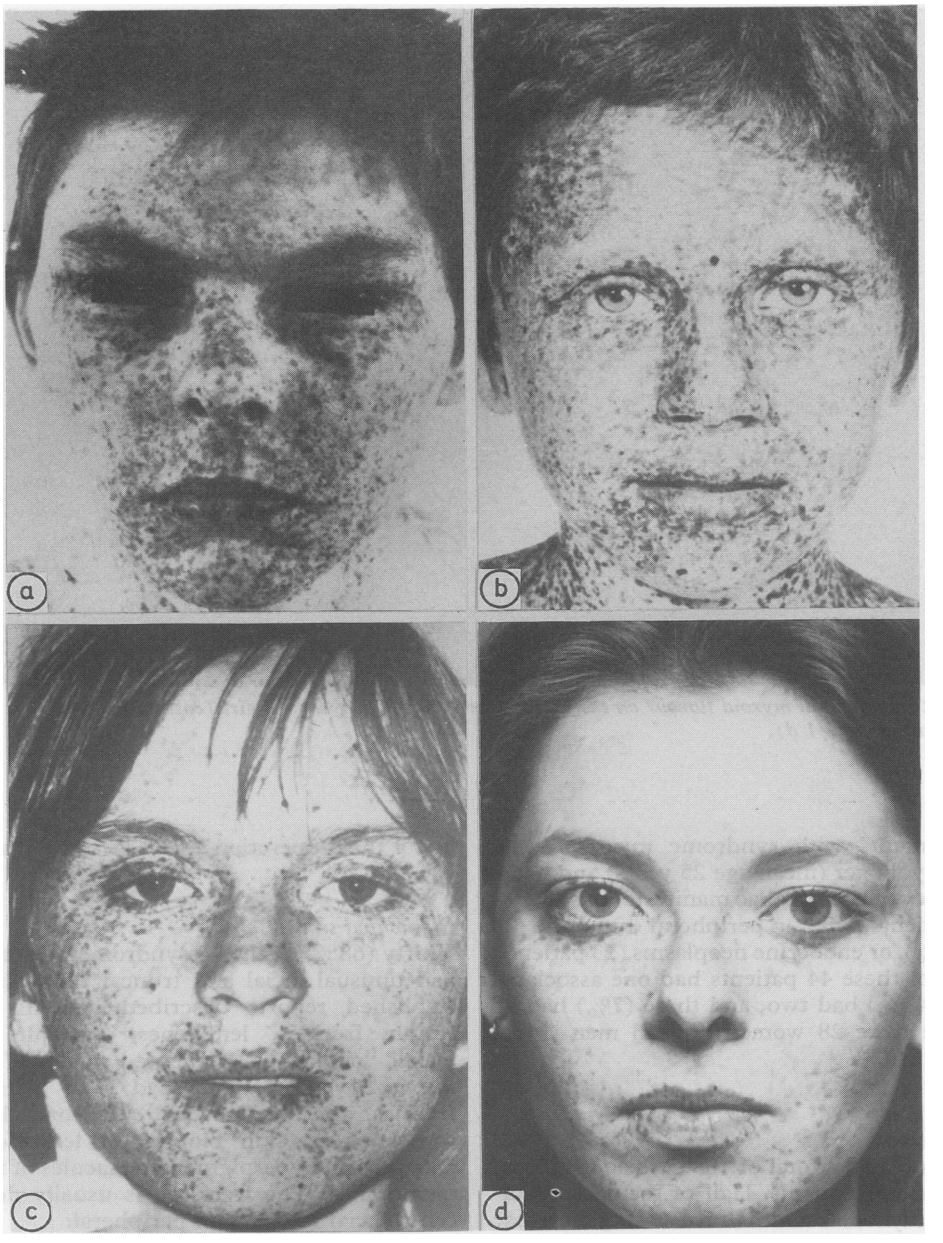

Fig 1 *Unusual facial freckling in four patients with atrial myxoma. (a) Eighteen year old man (case 27) with extensive freckling, palatal myxoid neurofibroma, and reddish hair. (From Rees et al.*[27] *By permission of the British Heart Journal.) (b) Ten year old boy (case 4) with biatrial myxoma, freckling, skin myxoid neurofibromas, blue naevi, and rust red hair. (From Atherton et al.*[5] *By permission of the British Association of Dermatologists.) (c) Fourteen year old boy (case 23) with left atrial myxoma, lentigines, and red hair. (From Peterson and Serrill*[23]*; by permission of the American Academy of Dermatology, Inc.) (d) Seventeen year old girl (case 40) with biatrial myxoma; right atrial myxoma recurred at age 19. There were extensive freckling and skin myxomas.*

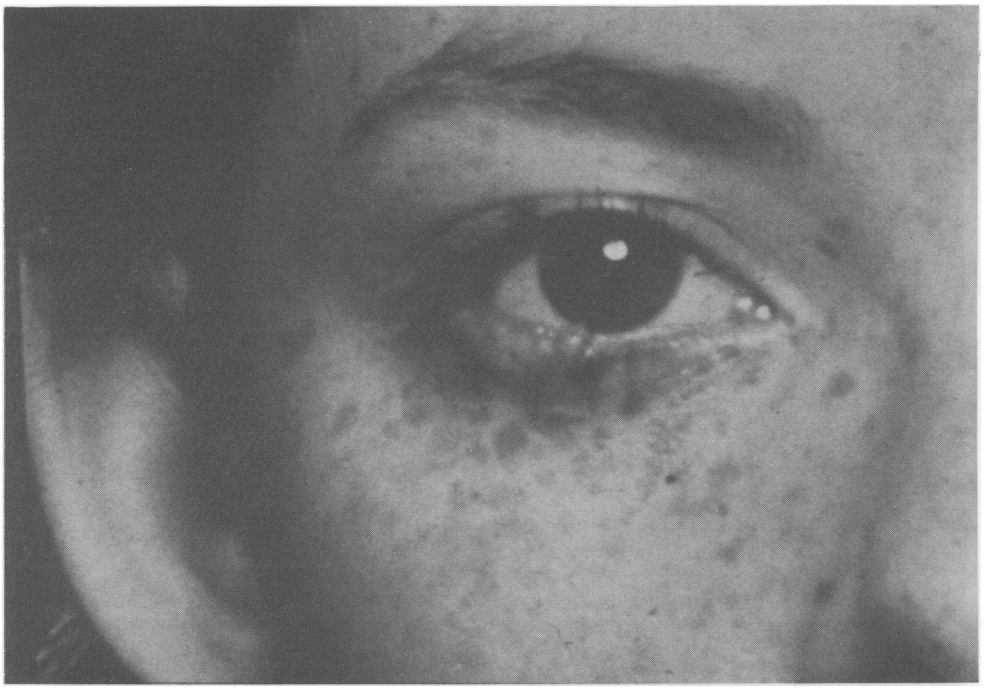

Fig 2 *Peripheral myxoid tumour on the lower right eyelid of 17 year old girl (case 40) (same patient as in fig 1 d).*

myxoma. Patients with syndrome myxoma were significantly younger (mean age 25 years) and had a high frequency of non-cardiac manifestations: freckling (30 patients, 68%), peripheral tumours (25 patients, 57%), or endocrine neoplasms (13 patients, 30%). Half of these 44 patients had one associated feature, 19 (43%) had two, and three (7%) had all three. There were 28 women and 16 men (ratio, 1·8:1).

Cardiac myxoma

The 44 patients had a total of 103 cardiac myxomas (2·3 myxomas per patient). Half of them had multiple cardiac myxomas and half had a single cardiac myxoma. In patients with single tumours, 41% were in the left atrium, 24% were in the right atrium, and 35% were in the ventricles. Twelve (27%) of the 44 patients had at least one ventricular myxoma.

Fifty two (50%) of the 103 tumours were in the left atrium, 32 (31%) were in the right atrium (10 were synchronous biatrial), 13 (13%) were ventricular (7 right and 6 left), and in six the affected chamber was unknown. Eight (18%) of the 44 patients had at least one recurrence of a cardiac myxoma and three had a third operation for recurrence (cases 10, 20, 41).

Pigmented skin lesions

Thirty (68%) of the 44 syndrome myxoma patients had unusual facial and truncal "freckling" (fig 1). Published reports described patients as having simple freckles, lentigenes, multiple superficial naevi, "cutaneous pigmented macules," and blue naevi. Several patients had both lentigenes and freckles. Each type of cutaneous lesion was confirmed by skin biopsy. At least four of the patients had hyperpigmented macules of the mucous membranes. The freckling is usually described as centrofacial rather than peripheral.

Peripheral tumours

Peripheral myxoid tumours (fig 2) or neurofibromas were present in 25 (57%) of the 44 patients; the sites included the breasts, face, extremities, torso, vulva, uterus, buttocks, and vocal cords. Two patients (cases 27 and 35) had neurofibromas of the palate. Histologically these tumours were myxomas, myxoid fibroadenomas, myxoid neurofibromas, neurofibromas, and myxoid leiomyomas. Several

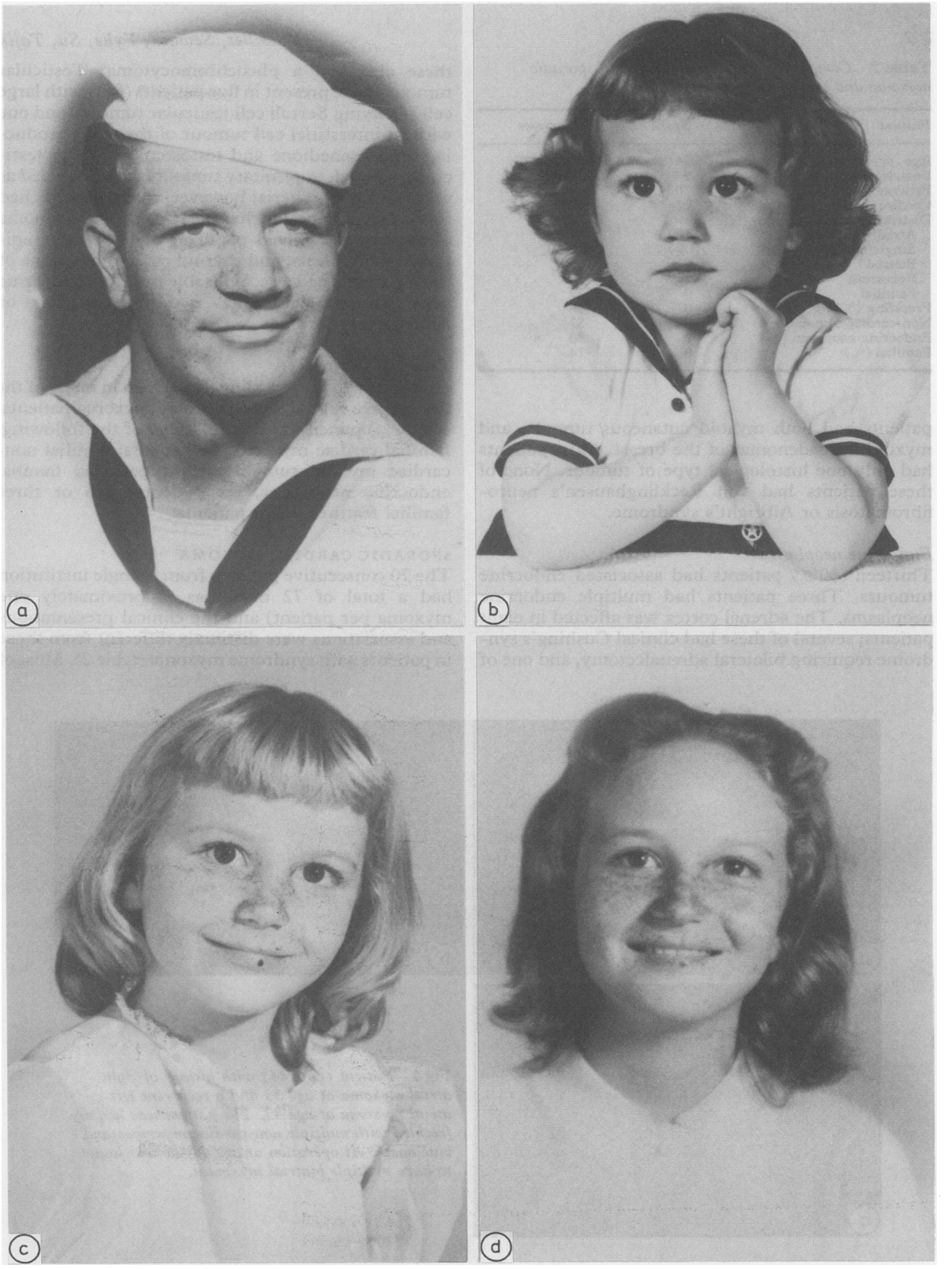

Fig 3 *(a) The father is pictured in his twenties; diffuse lentiginoses were present. He died at age 56 from a left atrial myxoma. His daughter (b, c, d) pictured at ages 2, 7, and 13 years, had diffuse lentiginoses that were apparent at a very early age and became more apparent with age. She died aged 21 after four operations for cardiac myxomas.*

Table 2 *Comparison of clinical features of sporadic myxoma and syndrome myxoma*

Feature	*Sporadic*	*Syndrome*
Age (yr) (range)	56 (39–82)	25 (10–56)
Female/male ratio	2·7:1	1·8:1
Patients (No)	70	44
Cardiac myxomas (No)	72	103
Distributions of myxomas (%):		
Atrial/ventricular	100/0	87/13
Single/multiple	99/1	50/50
Biatrial	0	23
Recurrent	0	18
Familial	0	27
Freckling (%)	0	68
Non-cardiac tumours (%)	0	57
Endocrine neoplasm (%)	0	30
Familial (%)	0	14

patients had both myxoid cutaneous tumours and myxoid fibroadenomas of the breast. Most patients had only one histological type of tumour. None of these patients had von Recklinghausen's neurofibromatosis or Albright's syndrome.

Endocrine neoplasms

Thirteen (30%) patients had associated endocrine tumours. Three patients had multiple endocrine neoplasms. The adrenal cortex was affected in eight patients; several of these had clinical Cushing's syndrome requiring bilateral adrenalectomy, and one of these also had a pheochromocytoma. Testicular tumours were present in five patients (four with large cell calcifying Sertoli cell testicular tumours and one with an interstitial cell tumour of the testis producing androstanedione and testosterone). Only testicular, adrenal, or pituitary tumours were regarded as valid for entry criteria; however, many patients had thyroid neoplasms, including Hürthle cell adenoma of the thyroid, mixed papillary and follicular epithelial hyperplasia, and thyroid carcinoma. None of these patients had a recognisable multiple endocrine adenomatosis syndrome, neurofibromatosis, or Albright's syndrome.

Familial features

In addition to the freckling (fig 3) seen in many of the first degree relatives of syndrome myxoma patients, 15 (34%) patients had at least one of the following: familial cardiac myxoma, 11 patients; familial non-cardiac myxoid tumours, eight patients; familial endocrine neoplasms, six patients; two or three familial features, eight patients.

SPORADIC CARDIAC MYXOMA

The 70 consecutive patients from a single institution had a total of 72 myxomas (approximately one myxoma per patient) and the clinical presentations and associations were distinctly different from those in patients with syndrome myxoma (table 2). Most of

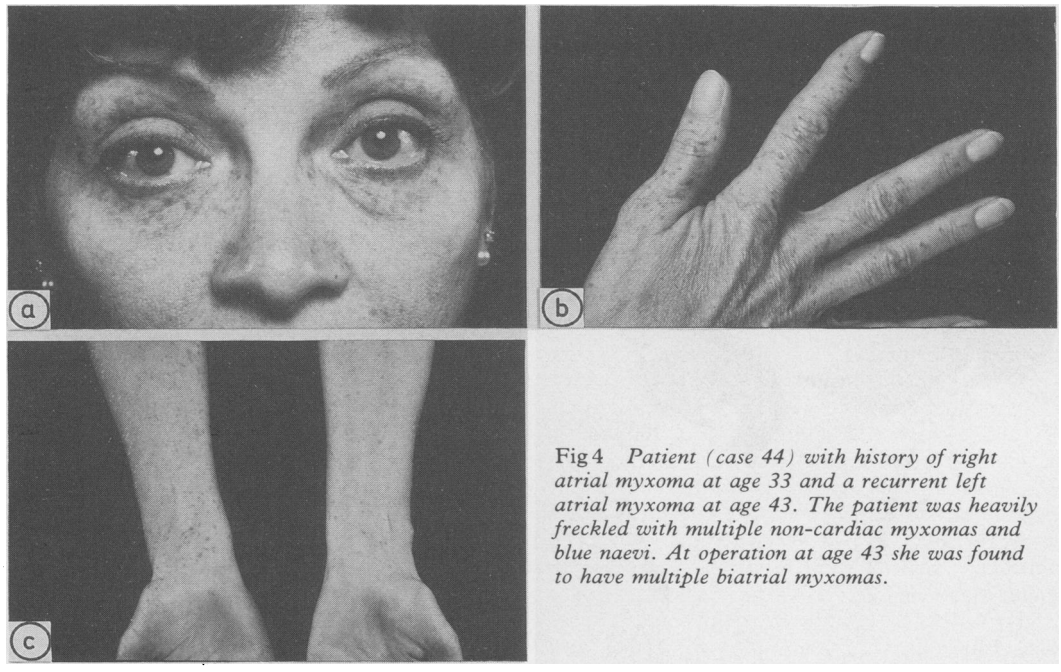

Fig 4 *Patient (case 44) with history of right atrial myxoma at age 33 and a recurrent left atrial myxoma at age 43. The patient was heavily freckled with multiple non-cardiac myxomas and blue naevi. At operation at age 43 she was found to have multiple biatrial myxomas.*

these patients have been reported elsewhere.[35-37] There were no bilateral or ventricular myxomas. There were no recurrences and no associated familial features. None of the patients with sporadic myxoma had unusual freckling or lentiginosis, peripheral myxoid tumours or neurofibromas, or adrenocortical or testicular tumours. The group comprised 51 women and 19 men (ratio, 2·7:1) with a mean age of 56 years.

Discussion

In 1960, Frankenfeld *et al* described a 22 year old white woman with "many dark brown to black freckles on the skin" and synchronous biatrial cardiac myxomas.[11] Although these investigators recognised the rarity of biatrial cardiac tumours, they did not appreciate the significance of the cutaneous hyperpigmentation. In 1973, Rees *et al* reported, in the *British Heart Journal*, the association of cutaneous lentiginosis and a left atrial myxoma in an 18 year old man (fig 1).[27] In 1980, Atherton *et al* described additional features—namely, peripheral tumours and blue naevi—in a 10 year old boy with a synchronous biatrial myxoma (fig 1).[5] In 1982, Schweizer-Cagianut *et al*, unaware of the reports by Rees *et al* and Atherton *et al*, described a single family with cardiac myxomas and familial endocrine neoplasms.[31] In 1984, Rhodes *et al* described another case and raised the question of the possible association of endocrine neoplasms and cardiac myxoma.[28] There had been earlier reports of cardiac myxoma and an association with fibroadenoma of the breast.[29] In 1984, we reported our observations on patients with cardiac myxoma and the belief that a subset of these patients represented a unique subgroup.[3] (In April 1984 this paper was the winner of the Associate Clinical Paper Competition at the meeting of the American College of Physicians in Atlanta.) Other investigators at the Mayo Clinic subsequently reported a review of the features of patients with a complex of myxomas, spotty pigmentation, and endocrine overactivity that included atrial myxoma.[26]

Previous descriptions of syndrome myxoma patients have usually appeared as isolated case reports. To date we have recognised five patients who originally presented at the Mayo Clinic and 39 gleaned from international reports. All 44 had cardiac myxomas; and this report is the first review to concentrate on syndrome myxoma patients with a cardiac myxoma.

A significant feature of this unique subgroup is young age (mean age, 25 *vs* 56 years), and the condition is typically associated with cutaneous lentiginosis, blue naevi, peripheral tumours, and endocrine neoplasms. It is not clear whether these patients have true freckles or lentiginosis; however, we favour the latter interpretation.

Approximately 50% of the patients with syndrome myxoma have multiple cardiac myxomas with a high frequency of biatrial, ventricular, and recurrent myxomas. In our review of published reports we found patient subgroups with cardiac myxoma in which syndrome features were common (syndrome/total): synchronous biatrial myxomas, 13/32 (41%)[38]; ventricular myxomas, 12/77 (16%); age <18 years, 15/66 (23%); recurrent cardiac myxomas, 7/33 (21%)[39]; multiple cardiac myxomas, 17/54 (31%)[39]; and familial cardiac myxomas, 12/30 (40%).[39]

The familial manifestations of the syndrome myxoma patients are particularly interesting. Of 12 reported families with familial cardiac myxoma,[7 9 12 16 25 31 32 40-44] seven (58%) had at least one family member with syndrome myxoma. For this presentation, we excluded relatives of syndrome patients with cardiac myxoma who failed to meet any of the three additional entry criteria (relatives in cases 9, 16, 31, and 32). It is strongly suggested, however, that these relatives are likely to have the syndrome.

This syndrome is probably a "genetic" disorder in the mendelian sense, but much more extensive family studies will be needed before a specific pattern of inheritance can be identified.[45] Individual cases of familial cardiac myxoma[45] may resemble cases of syndrome myxoma: patients with familial cardiac myxoma are younger and have a higher frequency of multiple, biatrial, and ventricular myxomas. For the present, however, the prudent physician should be aware of the possibility of familial occurrence and advise the first degree relatives (parents, siblings, and children) of patients with syndrome myxoma to be examined.

Theories about the pathogenesis of this syndrome remain speculative. Although we believe that syndrome myxoma is a separate entity, many other diseases can have some of the same characteristic features. Other cardiac syndromes with lentiginosis or freckling include electrocardiographic abnormalities,[46] valvar heart disease,[47] hypertrophic cardiomyopathy,[48] and the LEOPARD syndrome[49] (L = lentigenes, E = electrocardiographic conduction defect, O = ocular hypertension, P = pulmonary valve stenosis, A = abnormalities of genitals, R = retardation of growth, and D = deafness). Other entities such as von Recklinghausen's neurofibromatosis,[50] centrofacial lentiginosis,[51] multiple endocrine neoplasia type 3,[52] LEOPARD syndrome,[53] and Peutz-Jeghers[54] syndrome are associated with diffuse lentiginosis and endocrine

abnormalities and have an autosomal dominant mode of inheritance. Albright's fibrous dysplasia[55] and neurofibromatosis[56] are associated with hyperpigmented skin lesions, endocrine abnormalities, and soft tissue myxomas. Unlike most of these similar conditions, which are the result of a mutation in the embryonic neural crest,[56 57] myxomas are believed to be of mysenchymal origin. A recent report, however, suggests the possibility of maldevelopment of the neural crest in cardiac myxoma.[58]

We have avoided the use of mnemonic acronyms such as NAME[5] (N = naevi, A = atrial myxoma, M = mucocutaneous myxomas, E = ephelides) or LAMB[28] (L = lentigines, A = atrial myxoma, M = mucocutaneous myxomas, B = blue naevi) to describe the features of syndrome myxoma. Such acronyms describe only some of the manifestations of the syndrome, which appears to be a multisystem condition that may be associated with cardiac myxoma. We therefore believe there is no suitable acronym.

In summary, syndrome myxoma should be suspected in any patient under age 40 years with a cardiac myxoma at a site other than the left atrium. Such patients should be assessed preoperatively for important associations including adrenal integrity, and the surgeon should be made aware of the need for thorough inspection of the heart for multiple subclinical myxomas. Any patient who has familial, recurrent, ventricular, or multiple cardiac myxomas and is unusually freckled or has peripheral noncardiac myxomas or a rare endocrine neoplasm should be followed because syndrome myxoma often recurs. If syndrome myxoma is recognised in an individual, all the first degree relatives should undergo formal evaluation. Cardiac myxoma appears to be only one of the many manifestations of syndrome myxoma.

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