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ROLE OF THYMECTOMY IN MYASTHENIA GRAVIS

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ABSTRACT

Thirteen patients with myasthenia gravis underwent total thymectomy between January, 1988 and December, 1991. The duration of symptoms prior to surgery varied from 2 months to 20 years. In a follow-up ranging from 2 months to 4 years, 11 patients showed a significant improvement with either complete discontinuation of medication of a marked reduction in doses. One patient with a small benign thymoma showed some improvement but subsequently required stepping up of anticholinesterase medication and addition of steroids and immune suppressants; another patient with atrophic thymic tissue had complete remission after thymectomy but developed myasthenic symptoms six months later requiring medication again. Thymectomy is recommended for all patients with generalised myasthenia gravis with or without thymoma regardless of the duration of disease unless the patient is a very high risk candidate for surgery. It is not recommended for isolated ocular myasthenia gravis. (JPMA 42:107, 1992).

INTRODUCTION

Although the symptoms of myasthenia gravis were described in 1672[1], prior to the introduction of anticholinesterase drugs the disease was only recognized because of severe weakness and was fatal within a short period of time. The association of myasthenia gravis and thymic tumours was first made by Weigert in 1901[2]. Thymectomy for the treatment of thymomas and of myasthenia gravis was first introduced by Blalock and associates in 1939 and 1941[3,4]. This report describes our experience of surgical management of myasthenia gravis.

PATIENTS AND METHODS

Clinical data

From January, 1988 to December, 1991 thirteen patients underwent thymectomy for myasthenia gravis. Ages ranged from 15 to 50 years with a mean age of 30.5 years. Myasthenia gravis had been present for 2 months to 20 years with a mean duration of 4.5 years. Six were males and seven females (Table I).

Table I. Age, sex and duration of disease in 13 patients undergoing thymectomy.

S.No.	Name	Age/Years	Sex.	Duration of myasthenia before thymectomy
1.	QMH	50	Male	2 months
2.	SMA	50	Female	2 years
3.	JHR	15	Female	8 years
4.	CSI	21	Female	1 year
5.	KFA	32	Male	6 months
6.	WFA	32	Female	6 months
7.	CM	23	Male	9 years
8.	AAHK	40	Female	6 months
9.	JMA	21	Male	1 year
10.	RR	30	Female	4 years
11.	ZR	40	Female	9 years
12.	KNM	21	Male	3 years
13.	SAR	22	Male	20 years

All patients had moderate to severe generalised myasthenia gravis (Osserman classification Class II and III)5 and were moderately incapacitated in daily living and work. All patients were given anticholiriesterase medication pre-operatively and 6 were taking steroids prior to surgery. Three patients also had plasmapharesis on several occasions. The preoperative medications were determined by the referring physicians and were not changed prior to surgery (Table II)

Table II. Medications before Thymectomy.

S.No.	Name	Anticholinesterase drugs	Steroids	Imuran
1.	QMH	Mestinon 960 mg/day	Deltacortil 120mg /alternate days.	100mg/day
2.	SMA	Mestinon 240 mg/day	-	-
3.	JHR	Mestinon 360 mg/day	Deltacortil 30mg /day.	--
4.	CSI	Mestinon 820 mg/day	Delacortil 80mg /day &40 mg/day on alternate days.	-
5.	KFA	Mestinon 360 mg/day	Prednisone 15 mg BD or 10 mg on alternate days.	-
6.	WFA	Mestinon 480 mg/day	-	-
7.	CM	Mestinon 600 mg/day	Prednisone 25 mg/day	-
8.	AAHK	Mestinon 240 mg/day	Dexamethasone 5 mg on alternate days.	-
9.	JMA	Mestinon 240 mg/day	-	-
10.	RR	Mestinon 1080 mg/day	-	-
11.	ZR	Mestinon 180 mg/day	-	-
12.	KNM	Prostigmine 180 mg/day Mestinon 60 mg/day	-	-
13.	SAR	Prostigmine 240 mg/day	-	-

No attempt was made to add steroids if the patient was not already taking them. In the first 8 patients all medications were continued at the same dose immediately post-operatively and were gradually tapered off during the follow-up period using clinical improvement as an indicator. In the last 5 patients anticholinesterase drugs were begun at half the preoperative dose at least 12 hours after thymectomy

and were then adjusted according to the clinical response of the patient. Three patients had proved thymomas, 6 had lymphoid hyperplasia and 5 had involuted thymic tissue. In 5 of these patients lymphoid aggregates were found in the extrathymic anterior mediastinal fat. In one of the patients with a thyrnoma no other thymic tissue was evident (Table III).

Table III. Histopathology of thymus and mediastinal fat specimens in 13 patients undergoing thymectomy.

S. No.	Name	Thymoma	Thymus histology	Mediastinal fat and lymph nodes
1.	QMH	Lymphocytic thymoma	-	Lymphoid aggregates on re-exploration
2.	SMA	Lymphocytic thymoma	Involuted thymus	Lymphoid aggregates
3.	JHR	None	Lymphoid hyperplasia	-
4.	CSI	None	Lymphoid hyperplasia	Lymphoid aggregates
5.	KFA	None	Lymphoid hyperplasia	-
6.	WFA	None	Lymphoid hyperplasia	-
7.	CM	None	Severely involuted thymus with focal bony metaplssia	-
8.	AAHK	Mixed hyalinised lymph-epithelial thymoma	No thymic tissue seen	Lymphoid aggregates
9.	JMA	None	Lymphoid hyperplasia	-
10.	RR	None	Severely involuted thymus	-
11.	ZR	None	Moderately involuted thymus	Tuberculosis in lymph nodes.
12.	KNM	None	Lymphoid hyperplasia	Lymphoid aggregates
13.	SAR	None	Mildly involuted thymus	-

Surgical considerations

A complete median sternotomy was used through a midline vertical skin incision as the primary approach in all patients. The first patient had a simple thymectomy but 21 months later was re-explored and a clean out of the anterior mediastinal and anterior cervical fat was carried out. In the other 12 patients following wide exposure of the mediastinum not only all the thymic tissue, but also all suspected thymic tissue and anterior mediastinal fat were excised. The dissection was routinely carried laterally to the phrenic nerves or beyond and inferiorly to the diaphragm. Occasionally thin sheets of thymic tissue were initially misinterpreted as being normal pleura, and almost always while peeling mediastinal fat from the pleura and phrenic nerves, one or both pleural cavities

were entered. Mediastinal and pleural chest tubes were used routinely. Great care was taken to prevent injury to the phrenic nerves and none of the patients demonstrated diaphragmatic paralysis following thymectomy. The transcervical approach was avoided because of the possibility of phrenic nerve injury, of significant bleeding in the depth of the mediastinum in areas of compromised visibility and because a clean out of the entire anterior mediastinal fat is technically difficult through this approach. The importance of the latter to prevent leaving behind islands of thymic tissue has been demonstrated by Jaretzki and associates[6]. Extubation was achieved in 11 patients after thymectomy; of these two patients required reintubation and ventilatory support but were weaned successfully 6 days and 7 days later respectively from the ventilator. Two other patients were electively ventilated for 1 and 3 days respectively. Tracheostomy was not needed in any patient in this series.

RESULTS

Subsequent to a thymectomy the patients can be categorized as follows: remission - no symptoms and no medication; improved - less medication and better control of symptoms; same - equivocal improvement; worse - more medication, and symptoms unchanged increased 9. Using these criteria 3 patients went into remission, 1 patient went into remission for the first 5 months but subsequently developed fluctuating weakness requiring medication, and was therefore reassigned to the equivocal group, 8 patients were improved and 1 patient became worse. Benefit from the operation was thusachievedin 11 out of 13 patients (84.6%) (Table IV).

Table IV. Results of thymectomy

	No. of patients
Remission	3
Improved	8
Worse	1
Same	1
Benefit from operation	84.6%

Thymomas were present in 3 patients in this group (Figures 1 & 2).

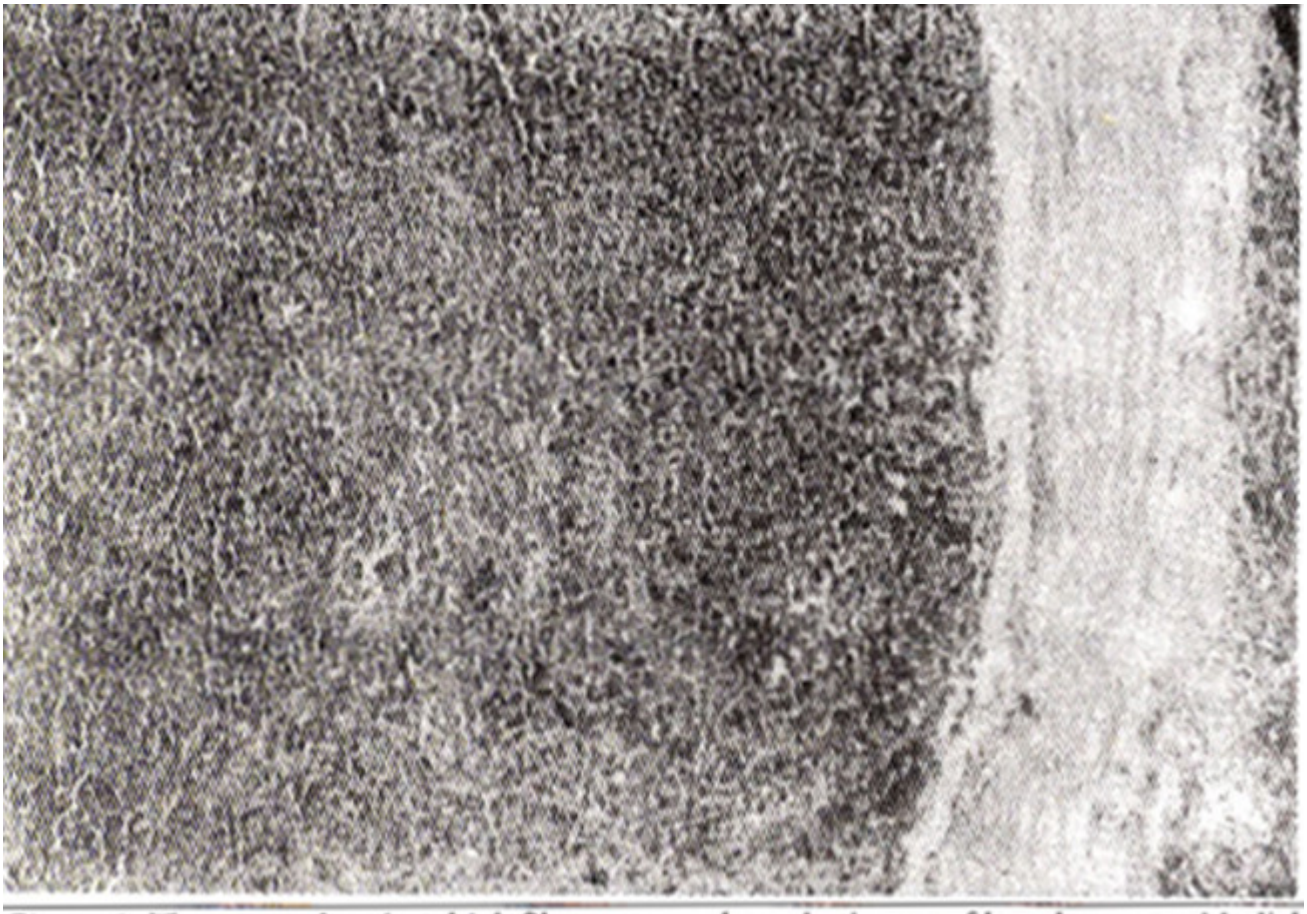

Figure 1. Thymoma showing thick fibrous capsule and mixture of lymphocyte-epithelial cells (H&E x 16).

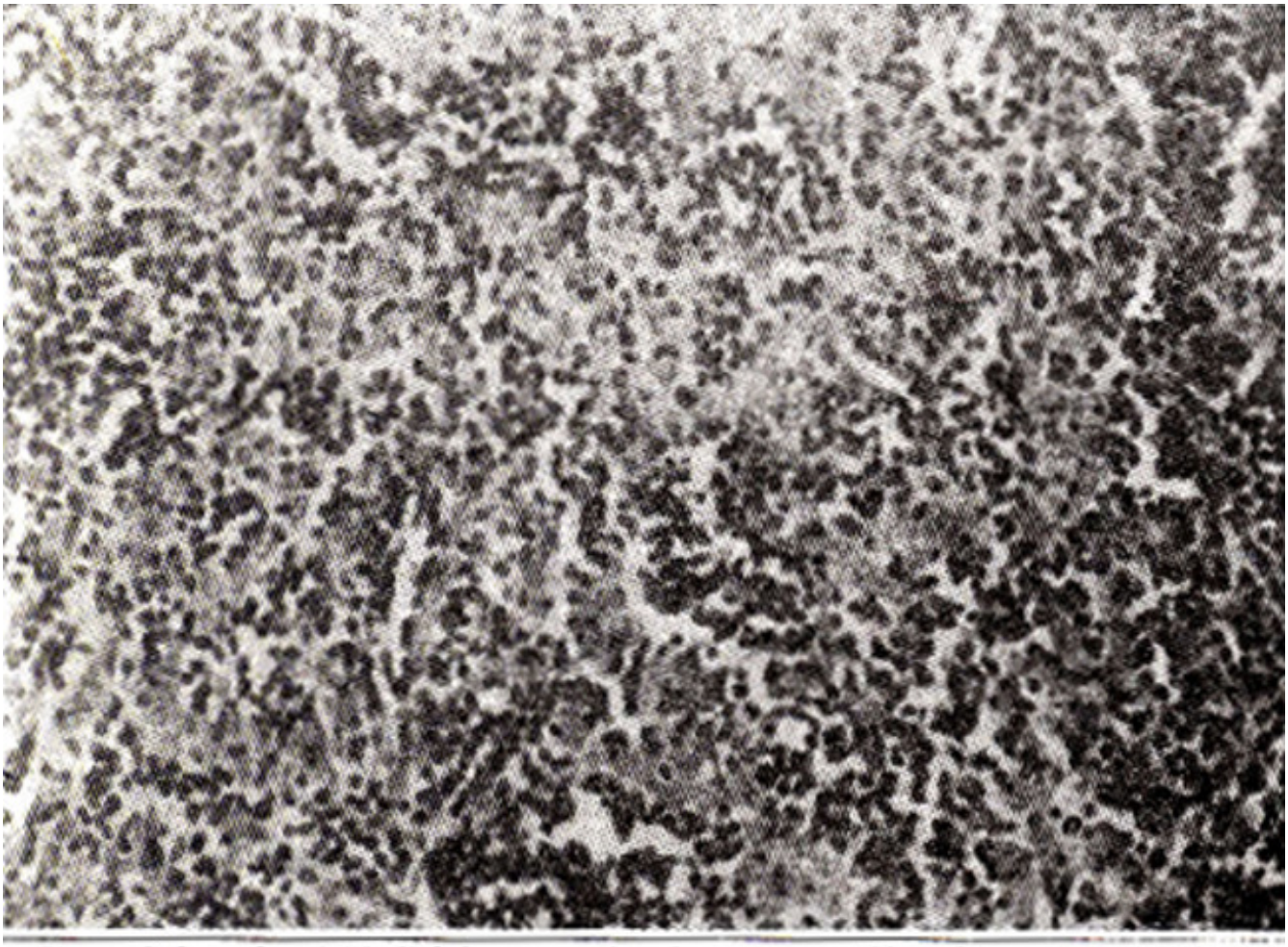

Figure 2. Lympho-epithelial thymoma showing mixture of lymphocytes and epithelial cells with open chromatin pattern (H&E x 400).

One patient (QMH) had a large invasive thymoma at the time of original thymectomy in January, 1988. The thymectomy was followed by a severe exacerbation of the myasthenia. Twenty-one months later a second exploration of the neck and mediastinum was done to completely remove all anterior mediastinal and cervical fat to eliminate any residual islands of thymic tissue as suggested by Jaretzki et al6. Although no recurrence of the thymoma was found, and no thymic tissue was identified on random histopathological sampling of the rather extensive amount of mediastinal and cervical fat removed, in view of the patient's significant improvement over 25 months of follow-up it is highly probable that microscopic islands of thymic tissue have indeed been eliminated. Lymphoid aggregates were identified in the mediastinal fat in this patient and may well have been responsible for perpetuation and worsen. ing of his myasthenia following the initial thymectomy. He has now gone into complete remission and requires no medication. The second patient (SMA) was found to have asmall thymomaand a small involuted thymus. After an initial mild improvement the course of myasthenia in this patient was exacerbated, leading to the addition of steroids and azathioprine (Imuran) and to a higher dose of pyridostigmine (Mestinon) to keep her moderately symptom free over a 24 month follow-up period. The third patient (AAHK) had a mixed lympho- epithelial thymoma but has shown significant improvement in 16 months of follow- up. In 6 patients where lymphoid hyperplasia of the thymus was the primary pathology (Figure 3),

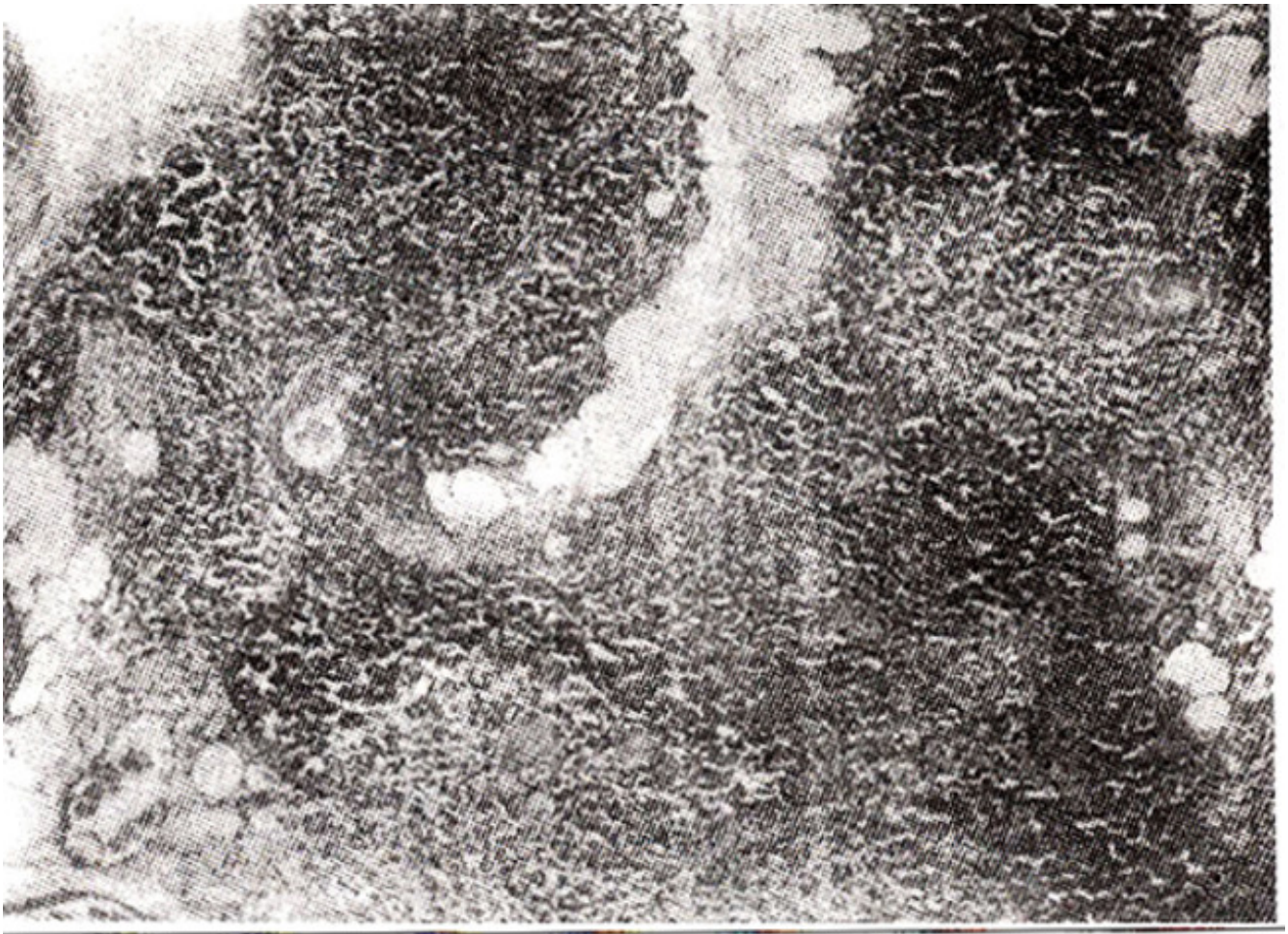

Figure 3. Thymus showing large number of lymphoid follicles with prominent germinal centers. small cellular hassel's corpuscles are also seen (H&E x 40).

thymectomy uniformly led to improvement in the symptoms of myasthenia gravis and to a decrease in medication requirements. Five patients were found to have an involuted thymus on histopathology (Figure 4).

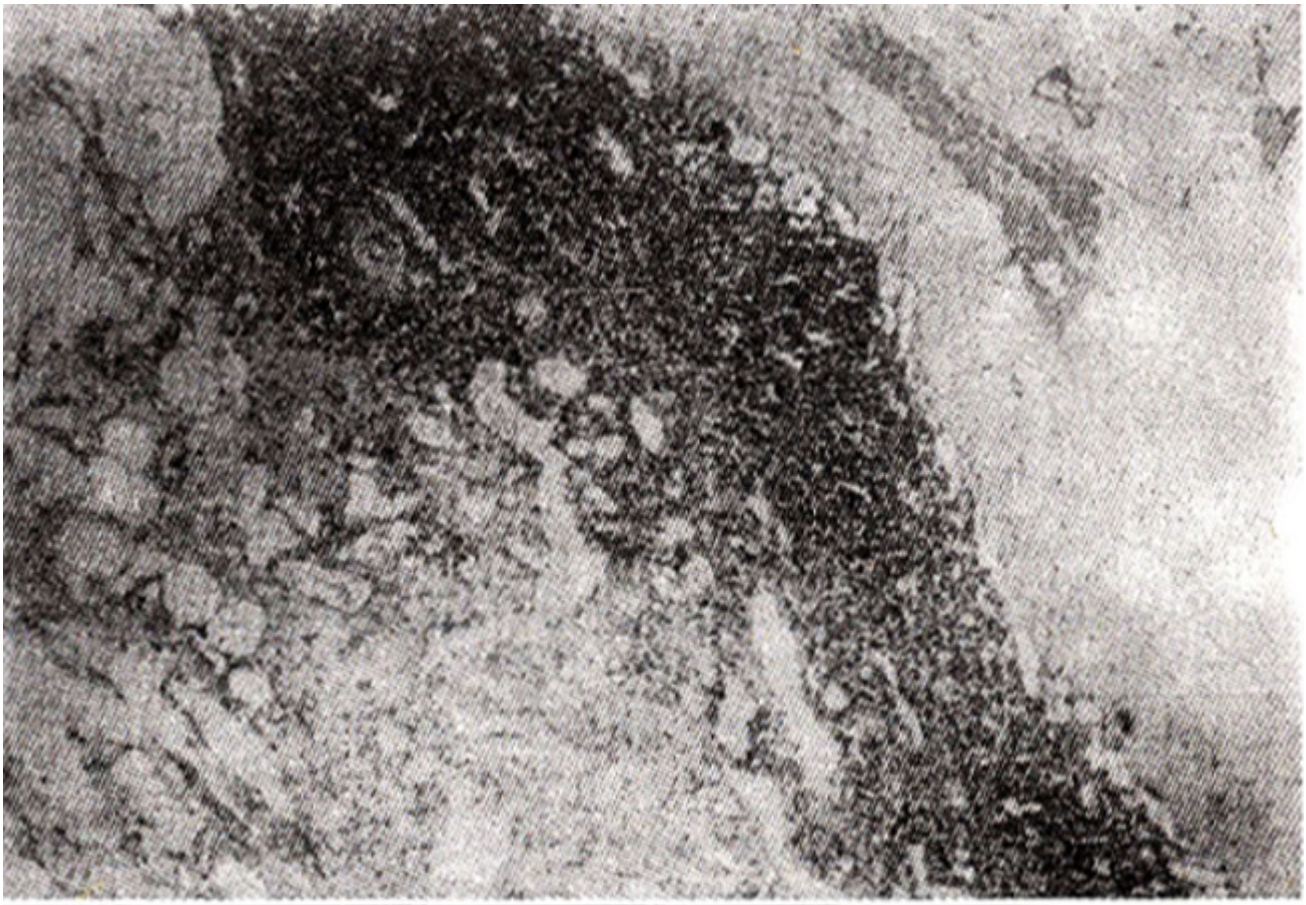

Figure 4. Grossly atrophic thymic tissue mainly composed of adipose tissue (H&E x 40).

One of these went into remission initially, became symptomatic again 5 months later and is now symptomatically almost the same as prior to surgery (Table V).

Table V. Medications and follow-up status after thymectomy.

S. No.	Name	Anticholinesterase drugs	Steroids	Imuran	Status	F/U
1	QMH	-	-	-	In remission	28 months re-exploration
2	SMA	Mestinon 300 mg/day	Predinisone 40 mg/day	50 mg/day	Moderate weakness	24 Months
3	JHR	-	-	-	In remission	22 months
4	CSI	-	Deltacortil 10 mg/day	-	Asymptomatic normal strength	17 months
5	KFA	Mestinon 300 mg/day	Deltacortil 10 mg on alternate days	-	Improved strength	16 months
6	WFA	Mestinon 90 mg/day	-	-	Asymptomatic normal strength	16 months
7	CM	Mestinon 240 mg/day	-	100 mg/day	Had remission for 5 months now fluctuating weakness but improved	16 months
8	AAHK	Mestinon 120 mg/day	-	-	Improved strength	16 months
9	JMA	Mestinon 180 mg/day	-		Improved strength	8 months
10	RR	Mestinon 720 mg/day	-	-	Improved strength	4 months
11.	ZR	Mestinon 120 mg/day	-	-	Asymptomatic normal strength	3 months
12.	KNM	Mestinon 240 mg/day	-	-	Asymptomatic Normal strength	2 months
13.	SAR	Prostigmine 30 mg/day	-	-	Asymptomatic normal strength	2 months

Other 4 patients have shown significant improvement with decreased anticholinesterase requirements. Five patients had lymphocytic aggregates in the extrathymic mediastinal fat (Figure 5).

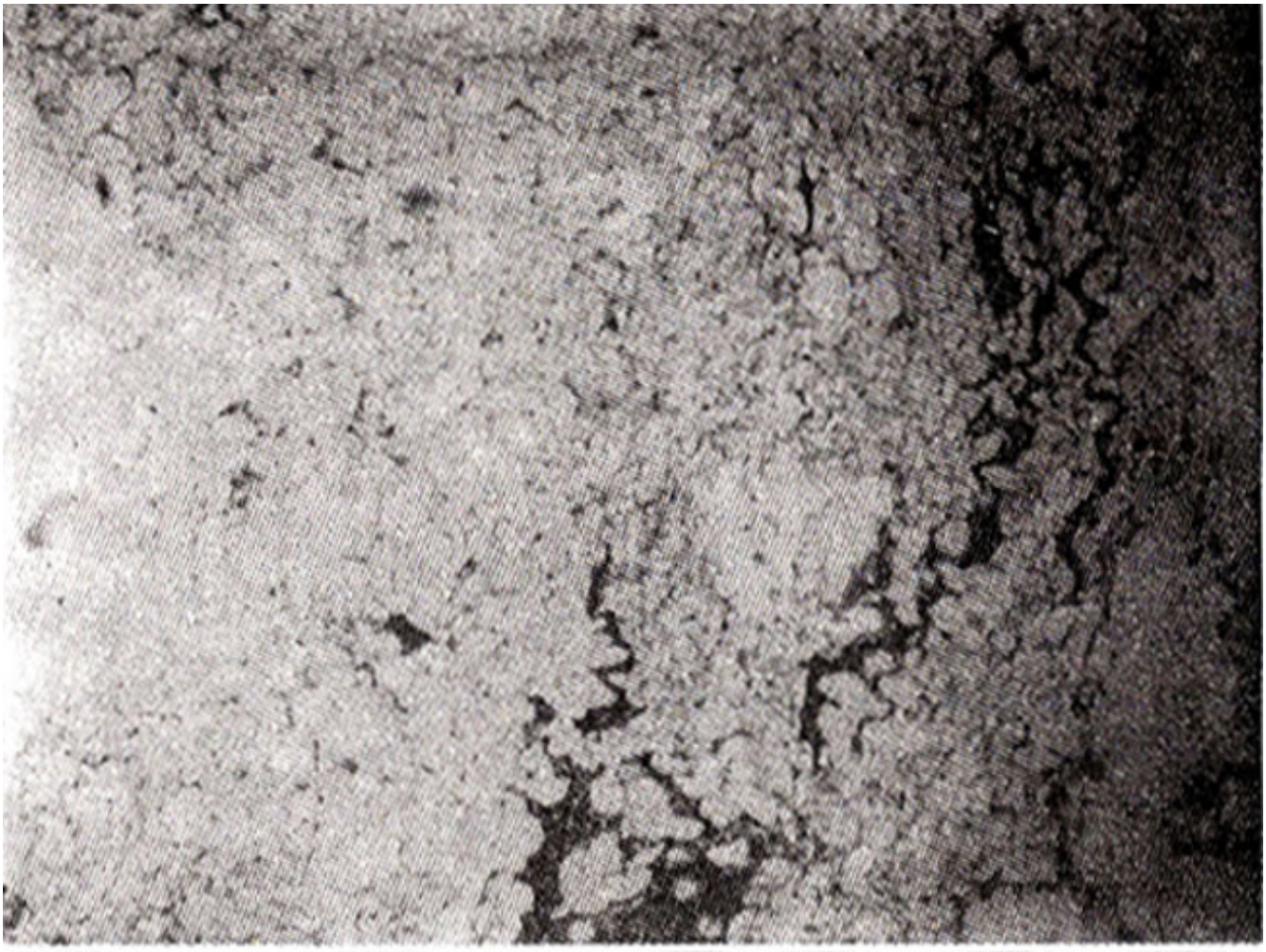

Figure 5. Mass of adipose tissue containing scattered small aggregates of lymphocytes (H&Ex16).

No Hassel's corpuscles were present in the aggregates and their exact significance with respect to myasthenia remains ill defined. One patient was found to have tuberculosis as an incidental finding in the anterior mediastinal lymph nodes removed at thymectomy and has required initiation of antituberculous treatment. The presence of tuberculosis did not appear to have an adverse effect on the myasthenic state of this patient or on her recovery following thymectomy. One patient developed a staphylococcal wound infection at the operative site which cleared on drainage and antibiotic therapy. No other complications occurred in this series.

DISCUSSION

It is well recognized that myasthenia gravis is an autoimmune disease, in the pathogenesis of which the thyrnus gland seems to play a central role, although the details of this role are not yet completely defined[7]. Weakness results from a reduction in acetylcholine receptors at the neuromuscular junction[8]. Despite significant advances in therapy myasthenia remains a potentially debilitating and life threatening disease. Currently 4 methods of treatment are available for patients with myasthenia: anticholinesterase drugs (Mestinon, Prostigmin) to enhance neuromuscular transmission; immune suppression (Prednisone, azathioprine) to decrease the immune response; plasmapharesis to remove some of the circulating autoantibodies; and thymectomy to remove a major source of antibody

production[9]. For this complex autoimmune disorder while all or any of the above modes of therapy may be necessary, it is now generally accepted that removal of the thymus gland is distinctly beneficial in the majority of patients with generalised myasthenia gravis[9,10]. It has also become gradually clear that for remission of myasthenia to occur the thymectomy must be :complete:, in that not only the thymus gland itself but all possible islands of thymic tissue should also be removed. In a series of elegantly carried out dissections, Jaretzki et al demonstrated that accessory thymic tissue occurs in unusual position in the neck and large amounts may be found in the anterior mediastinal fat away from the thymic lobes[10]. They have therefore, recommended a :maximal: thymecout through a mid-sternotomy and a separate transcervical incision. Recently Fukai et al from Japan have demonstrated the presence of accessory thymic tissue in the retrocarinal fat in 2 of 27 autopsy subjects although none was found in the fat anterior to the descending thoracic aorta[11]. The retrocarinal area is not accessible through a median sternotomy. This tissue therefore cannot be removed at the time of the initial thymectomy but should be explored in cases of recurrent myasthenia where a complete anterior mediastinal clean out has been previously performed and no evidence of thymoma can be seen on re-evaluation with a CT scan. Some of the factors which have been known to favourably affect the results ofthymectomy have been the presence of acetyicholine receptor antibody[9], the presence of hyperplasia in the thymus removed,the absence of a thymoma and a shorter duration of disease with milder symptoms[12]. A younger age group (second and third decades) and the female sex, previously considered favourable predictors, now appear not to affect the incidence of remission following thymectomy[12,13]. However, none of these factors are absolute indicators of the response to thymectomy in an individual patient. This is corroborated by the results of our series where age, sex, and the presence of thymic hyperplasia or involution did not effect the response to thymectomy. A study by Papatestas et al clearly demonstrates that thymectomy significantly influences the clinical course in patients with myasthenia gravis; compared with nonsurgical treatment thymectomy is followed by an earlier onset of remissions, a lower mortality, a delay in the appearance of extrathymic neoplasms and also appears to avert the progression of the disease[12]. Buchingham et al in a computer assisted matched study to assess the value of thymectomy in myasthenia gravis showed the distinct benefits of thymectomy as compared to medical treatment alone in a lower early mortality, a higher five year survival rate and in the induction of complete remissions[13]. Others[14] have also underscored the benefits of thymectomy in patients with myasthenia gravis. We have therefore adopted rather liberal criteria for selecting patients for thymectomy All patients with generalised myasthenia gravis are offered the operation unless the patient is medically unfit for surgery or the symptoms are minimal and the patient asymptomatic on small doses of anticholinesterase drugs. In patients with ocular myasthenia alone, thymectomy is not recommended because long term follow-up in these group IA patients (Osserman classification') has shown this to be an essentially benign condition which, except in rare instances, remains confined to the lids or ocular muscles[15,16]. In patients over the age of 55years thymectomy was previously discouraged because of the frequent observation of an atrophic involuted gland. In fact, the presence of atrophic involuted thymus may not preclude immunological activity since Dalakas et al[18] reported significant staining for thymosin alpha - 1 hormone in grossly atrophic thymic tissue, and Haynes et al[19] found altered T-cell subsets following removal of atrophic thymus. Although some controversy still exists regarding the performance of thymectomy through a median sternotomy versus a transcervical incision, the former has been exclusively used as the primary approach in this series since it allows a complete resection to be performed easily and safely. In the first 8 patients the anticholinesterase medication as well as steroids were started at pre-operative doses immediately after thymectomy. It was found however, that the 2 patients who required reintubation and ventilation were in cholinergic crisis. It has been shown that following thymectomy most patients develop increased sensitivity to the medication[9,17]. Our protocol therefore has now been modified to

resume medication no sooner than 12 hours postoperatively and to initially give only one half of the preoperative dose. This is then increased according to the individual requirement of each patient. The steroids however are continued at preoperative doses and then tapered over 4 to 6 months. Plasmapharesis prior to surgery is recommended in patients with very severe and rapidly progressive symptoms[9]. Three to six exchanges over a one to four weeks period allow for a much safer peri-operative course. Only two of the patients in this series had plasmapharesis although 2 others could also have benefited from it. In Pakistan at this time the inconsistency in the availability and the high cost of the plasmapharesis kits necessary for the procedure make it difficult to use this modality in our patients. In conclusion the distinct benefits of thymectomy as demonstrated by the experience of others and corroborated by our results make it a highly desirable therapeutic measure in the management of patients with myasthenia gravis.

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