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TEMPORAL RELATIONSHIP BETWEEN THE ONSET OF THYROID DERMOPATHY AND GRAVES' OPHTHALMOPATHY

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SUMMARY

Pretibial myxedema is an uncommon manifestation of *Graves' disease* and because of its rarity, information regarding its natural course and its relationship with other manifestations of *Graves' disease* is not sufficient.

We reviewed 150 consecutive cases diagnosed as having pretibial myxedema in a twenty-year period in a tertiary care center. Only one patient in this group did not have ophthalmopathy, and the majority of cases had significant proptosis and ophthalmopathy, 30% required orbital decompression surgery. Dermopathy is a late manifestation of the *Graves' disease* and its onset is usually after the diagnosis of hyperthyroidism and ophthalmopathy. In a few patients, dermopathy preceded diagnosis of hyperthyroidism or the onset of ophthalmopathy. Fourteen patients have never had hyperthyroid, eleven patients in this group had developed spontaneous hypothyroidism.

All cases showed the involvement of the lower extremities, and only one patient showed to have combined upper and lower extremities involvement. The most common form of thyroid dermopathy was non-pitting edema. Nodular and plaque forms were also relatively common and occurred with equal frequency. Polypoid form occurred in one patient and elephantiatic form in another. There was no consistent correlation among different types of dermopathy and severity of eye disease.

During a three-month to nineteen-year follow up in 120 patients, complete remission was observed only in twelve patients. Partial remission was more common and occurred more frequently in patients who had local steroid therapy.It is possible that patients with remission might have been excluded of the follow up program.Thus, the remission data should be interpreted cautiously.

KEY WORDS: *Graves' disease; Hyperthyroid; Myxedema; Ophthalmopathy; Proptosis; Thyroid; Thyroid dermopathy.*

INTRODUCTION

Pretibial myxedema or more appropriately thyroid dermopathy is a condition in which there is a localized thickening of the skin. It is almost always associated with infiltrative ophthalmopathy.

Although the association of pretibial myxedema (dermopathy) with *Graves'* hyperthyroidism has been known for a century, it has still remained a mysterious phenomenon. It is an ailment with relatively low frequency in *Graves'* patients and has a baffling anatomic location (lower legs and feet). Many questions about the relationship between pretibial myxedema and *Graves'* ophthalmopathy have to be answered. The natural course and the long-term effect of therapy are still unknown. The chronologic relationship between the two manifestations of dermopathy and ophthalmopathy has not been well documented yet.

In the present study, at first we will briefly discuss *Graves, disease and Graves'* ophthalmopathy, and then we will review the literature of pretibial myxedema. Finally, we will report an analysis of 150 cases of *Graves' disease* with pretibial myxedema at the Mayo Clinic in a twenty-year period.

OBJECTIVES OF THE STUDY

Pretibial myxedema is a known manifestation of *Graves' disease*; however, there is a paucity of information, regarding its natural course and effect of treatment. It is also generally believed that pretibial myxedema is almost always associated with *Graves'* ophthalmopathy, but its relationship with the severity of the eye disease has not been well documented, and its evidence is anecdotal.

We will report a twenty-year experience (1969-1989) with thyroid dermopathy from the Mayo Clinic with the following objectives:

A) to define clinical features and dermographic characteristics;
B) to clarify the chronological relationship between the onset of dermopathy and the diagnosis of hyperthyroidism;
C) to determine whether the presence of dermopathy indicates the severity of ophthalmopathy;
D) to determine the effect of local steroid therapy in the course of dermopathy;
E) to obtain information, regarding various clinical types of dermopathy and their relationship with the severity of the eye disease.

MATERIALS AND METHODS

We retrospectively reviewed all the records of the patients who were diagnosed to have thyroid dermopathy or pretibial myxedema between November, 1969 and May, 1989. Only the patients were included who had definite pretibial myxedema on the basis of clinical diagnosis according to an endocrinologist or a dermatologist. Negative biopsy or inadequate clinical description of the disease were the basis of the exclusion for pretibial myxedema. Out of 159 reviewed charts with the diagnosis of pretibial myxedema, nine patients were excluded, and thus 150 remaining cases were analysed.

An 85-point abstract sheet with specific attention to clinical characteristics of ophthalmopathy, dermopathy, various methods of therapy, and laboratory data was prepared for each patient. Krahn exophthalmometer readings as a measure of proptosis, visual acuity, measurement by Snellen's chart, visual field scotomas, diplopias, papilledema, and exposure keratitis were also documented. Ophthalmopathy was defined on the basis of clinical criteria and examination of an ophthalmologist. The treatment of *Graves'* ophthalmopathy included systemic steroids, transantral orbital decompression, retro-orbital radiation (only for one patient).

Detailed dermatological evaluation was available in almost all patients and according to the description of dermatologists, three major classes of thyroid dermopathy were identifiable.

1) **Non-pitting edema form:** This form was characterised by the presence of non-pitting

edema, hyperkeratosis, pigmentation, and a brownish-red discoloration of the skin. Plaque formation and nodularity were particularly absent in this group.

2) **Plaque form:** This form is consisted of the separate or confluent raised plaques.
3) **Nodular form:** This form was characterised by nodule formation.
4) Other less common forms were elephantiatic form and polypoid form (one case of each was observed).

Histological diagnosis was made by full thickness and punch biopsies performed by a dermatologist. The diagnosis of hyper or hypothyroidism was made by the usual thyroid function tests including sensitive TSH, free thyroxine, serum total thyroxine, and thyroxine binding globulin measurement. Thyroid stimulating immunoglobulin was measured by a method based on cyclic AMP generation on FRTL5 cell line.

Thyroid dermopathy is usually treated by the application of 1% triamcinolone under occlusive dressings with each course of therapy ranging from 2-10 weeks.

Follow up was done in 80% of the patients with a range of 1.4 to 19 years with the average follow up of 3±2 years. The follow up range from the time of the onset of dermopathy was 1.4-19 years with the mean of 7±2.6 years.

STATISTICAL METHODS

Student T-test and Qui-Square Tests were used when they were appropriate for statistical analysis to show the significance of the difference of the mean values.

RESULTS

Dermographics: Thirty-three patients were male (22%) with the mean age of 53.1 and range of 32-70. One hundred and seventeen patients were female (78%) with the mean age of 51.2 and range of 18-80. Female to male ratio was 3.5. The mean age for all the patients was 53.

Figure 1 shows relative frequency of patients per decade of life for males and females.

Clinical characteristics of patients with thyroid dermopathy: Tables 1 and 2 show the clinical characteristics of the patients at the time of the first Mayo Clinic visit, 110 patients were euthyroid (73%), 11 were hypothyroid (7%), and 23 were hyperthyroid (15.3%).

Fourteen patients (9.3%) have never had hyperthyroidism. Among them, 11 patients (7.3%) had spontaneous hypothyroidism. Three patients remained with euthyroid. Various methods of therapy were employed for the treatment of hyperthyroidism. The majority (105 patients, 70%) had received I-131 therapy, 32 patients (21%) had to be treated with a second dose of radioactive iodine, 11 patients (7%) had thyroidectomy followed by I-131 therapy, 12 patients (8%) had just been thyroidectomy, and eight patients received anti-thyroid medications (Table 2).

As shown in Table 1, the non-pitting form of pretibial myxedema was the most common form, 50% of the patients (76 patients) had non-pitting edema type of dermopathy. The nodular form was seen in 17% of the patients (n=26) and the plaque form in 18% of the patients (n=28). One patient had the polypoid form and another patient had elephantiatic form of pretibial myxedema. One hundred and seventeen patients (78%) had only bilateral pretibial myxedema, and 32 patients (21%) had their dermopathy on their feet and pretibial area in a symmetrical fashion. Only one patient had pretibial myxedema of the hands as well as feet and pretibial area.

Pathological findings: In all of the eighty patients examined through biopsy, pathology was consistent with pretibial myxedema with criteria outlined previously. For the seventy remaining patients, biopsy was not performed and a classic picture of thyroid dermopathy was the basis of diagnosis.

TSI index: Only six patients had thyroid stimulating immunoglobulin measurements and the TSI index was extremely positive for all of them.

OTHER MANIFESTATIONS OF *GRAVES' DISEASE*

Thyroid acropachy: Eleven patients (7.3%) had

acropachy based on clinical diagnosis of clubbing. In these patients, no other disease could explain the digital clubbing. Only one patient had radiological studies of the extremities, and in this patient subperiosteal reaction was observed.

Ophthalmopathy: All patients except one had clinical ophthalmopathy. Mean proptosis was 22.2 mm in the right eye with a range of 15-34 and 22.6 mm in the left eye with a range of 16-34. There was no significant difference between proptosis in males and females ($P>0.1$). Tables 3 and 4 show the characteristics of ophthalmopathy in patients with pretibial myxedema. Sixty-two patients (41.6%) had diplopia and 42 patients (28.1%) had reduced visual acuity. Ophthalmopathy was usually severe. Orbital decompression was performed in 45 patients (30.2%). The operation was unilateral in 12 patients (27%) and bilateral in 33 (73%). Thirty patients (20%) had their orbital decompression surgery at the Mayo Clinic. The surgical procedure was transantral orbital decompression. In the transantral orbital decompression the floor and the median wall of the orbit and the ethmoid sinuses were removed via the maxillary sinus without any external surgical scar. The characteristics of ophthalmopathy in patients with and without the need for transantral decompression are shown in Table 5.

Temporal relationship between the onset of thyroid dermopathy and *Graves'* ophthalmopathy: It is evident from Figure 2 that thyroid dermopathy can occur before or after the onset of ophthal--mopathy, but it usually occurs after the onset of ophthalmopathy. Seventy-eight per cent of the patients had their onset of dermopathy after the onset of ophthalmopathy and only 22% developed dermopathy prior to ophthalmopathy. The majority of cases developed dermopathy within the first two years after ophthalmopathy (67.6%). However, some cases of dermopathy occurred fourteen years after the development of ophthalmopathy. Thirteen per--cent of dermopathies developed within two years prior to ophthalmopathy and, likewise, some patients developed dermopathy up to ten years prior to the development of ophthalmopathy.

The time interval between the diagnosis of hyperthyroidism and the onset of symptoms of dermopathy and ophthalmopathy is shown on bar graphs 3 and 4. Arbitrarily, symptoms, occurring within three months before and after diagnosis, were considered to occur simultaneously with hyperthyroidism. Because of patients' inability to pinpoint the time of onset, the date of the diagnosis of hyperthyroidism was chosen as a reference, since it was a more accurate time point than the time of the onset of symptoms of hyperthyroidism. Hyperthyroid symptoms, at the onset, are more non-specific and insidious than ophthalmopathy and dermopathy.

The peak of frequency of the onset time for *Graves'* ophthalmopathy was 0-12 months after the diagnosis of hyperthyroidism and for thyroid dermopathy 12-24 months after the diagnosis of hyperthyroid. In 34% of the patients, *Graves'* ophthalmopathy appeared beyond the first year after the diagnosis of hyperthyroid as opposed to 66% for the onset of thyroid dermopathy.

The relationship of ophthalmopathy manifestations with clinical forms of pretibial myxedema: Pertinent manifestations and characteristics of ophthalmopathy, occurring in different forms of pretibial myxedema have been shown in Table 6. It is clear that proptosis was significantly less pronounced in the non-pitting form of thyroid dermopathy. The frequency of diplopia was similar in all three groups. The need for aggressive therapy for ophthalmopathy such as steroid or surgical decompression was more in the non-pitting edema group. However, surprisingly, this group had more chance of developing exposure keratitis; the same group had the higher chance of developing reduced visual acuity.

THE OUTCOME OF THYROID DERMOPATHY WITH AND WITHOUT TREATMENT

The mean interval between the onset of dermopathy and the last Mayo Clinic visit was 7 ± 2.6 years (Table 7). Twelve patients underwent complete remission (10%). Thirty-seven patients developed partial remission of dermopathy (30%). Figure 4 shows the percentages of patients undergoing combined partial or complete remission at different

intervals after the onset of dermopathy.

The effect of treatment and the rate of partial remission: Seventy-six patients (63%) received local steroid therapy. The therapy was intermittent and the duration of therapy ranged from 2.5 months to 5 years. Due to a small number of patients with complete remission, the patients could not be stratified into the treatment and non-treatment groups. However, when the rate of partial plus total remission of patients of the two groups during the follow up examination was analysed, the remission rate was higher in the earlier stage of disease.In the local steroid group, 28 patients (18%) had partial remission in the follow up as opposed to 8 patients (18%) in the non-treatment group (76 patients with steroid therapy and 44 patients with no therapy were at least three months being followed up).

DISCUSSION

Since pretibial myxedema is rare, large scale studies are possible only in the tertiary care centers. We reviewed the related literature and as we know, the present study is the largest group eversince being reported. Our cases represent all of the patients with pretibial myxedema and *Graves' disease* who were diagnosed to have pretibial myxedema as one of the final dismissal diagnoses. Thus, it is conceivable that in the same twenty-year period more cases of pretibial myxedema may have been observed but not indexed. However, we believe that this report includes the majority of cases being observed within the twenty-year period.

It has been stated that pretibial myxedema occurs in older patients(1). In our group, the mean age was 53 and the male and female ratios and age distribution were not different from the general population of patients with *Graves' disease*. For the Mayo Clinic patients, the most common age group for *Graves' disease* and ophthalmopathy was 50-60 years (Fatourechi, unpublished data). This is similar to the age distribution of patients with pretibial myxedema. Mayo Clinic patients might have possibly higher mean age because of the referral nature of the practice. In fact, patients with *Graves' disease*from Rochester, Minnesota, were younger (Fatourechi, unpublished data).

Similar to ophthalmopathy, pretibial myxedema can occur in the absence of clinical thyroid dysfunction(2). Lynch and colleagues collected 19 cases of euthyroid pretibial myxedema and added four cases of their own to them(2). It is interesting that eleven patients in our group have never had hyperthyroid and have developed spontaneous hypothyroidism and a separate group of three patients had no history of thyroid abnormality. It is interesting to find out whether the autoimmune pattern and the thyroid antibodies were more different in the hyperthyroid group than in the group without a history of hyperthyroidism. It is possible that the patients with hypothyroidism may have thyroid blocking antibodies rather than thyroid stimulating antibodies. These studies were not applicable on our patients and in fact only six patients had thyroid stimulating antibody measurements, all being positive regardless of their thyroid function status.

The question which has been raised but never been proved is that I-131 therapy may aggravate ophthalmopathy. It has been suggested that treatment with steroids at the time of radioactive iodine-therapy may prevent aggravation of the eye disease(3). Whether or not it is true with pretibial myxedema has not been investigated. Seventy per cent of our patients had one course of treatment with radioactive iodine-therapy and 21% required a second dose of radioactive iodine. This is the representative of the general population of patients with hyperthyroid *Graves' disease* who were treated at the Mayo Clinic. Five per cent had just anti-thyroid therapy. The majority of patients were given high doses of radioactive iodine; consequently, they became hypothyroid within three months and were led for thyroxine therapy. Thus, the effect of the methods of therapy in the development of severity of pretibial myxedema could not be predicted from the present series.

The reason for localization of thyroid dermopathy in the pretibial area has not been explained. Stasis and trauma have been implicated. Various other foci of dermopathy in the *Graves' disease* have been reported(4,5). It has also been suggested that even in the absence of clinical dermpathy, abormal mucopolysaccharide deposition in the foream of patients with pretibial myxedema is

present(6). Systematic biopsies of all patients with *Graves' disease* in the lower extremities and also biopsy of the upper extremities in patients with *Graves' disease* associated with pretibial myxedema will be interesting to show if subtle collagene tissue abnormalities can be demonstrated in a larger group of patients. In our series, only one patient had clinical upper extremities involvement.

Although various clinical forms of non-pitting edema, plaque form, and other forms for thyroid associated dermopathy have been described, the relative frequency of these forms has not been reported previously. Fifty per cent of the patients in our group had non-pitting edema type, 17% had nodular, and 18% had plaque form. Thus, the non-pitting edema appears to be the most common form of thyroid dermopathy. Polypoid and elephantiatic form of dermopathy probably represent more advanced cases of nodular pretibial myxedema. These latter forms are extremely rare and the incidence rate of our series was less than 1%. Reviewing the pathology reports of 80 patients in our group did not show any distinguishing characteristics of various clinical forms of dermopathy. For 70 patients, pathology confir--mation was not available. In these patients, the possible reason for not obtaining a biopsy was a classic clinical presentation. The less typical cases were more likely to have pathologic confirmation.

It has been reported anecdotally that almost all patients with pretibial myxedema usually have ophthalmopathy and especially severe ophthalmo--pathy. In our group of 150 patients, only one patient did not develop ophthalmopathy during a long follow up period. The majority of patients developed dermopathy after to the onset of ophthalmopathy. However, in 12% of our patients, the onset of dermopathy was prior to significant ophthalmopathy. In these patients, dermopathy occurred any time from 1-8 years prior to the development of ophthalmopathy. We cannot ignore the fact that ophthalmopathy of subtle degree was not present at the onset of dermopathy in these patients, since it is possible that the patients had failed to observe the changes.

In the previous report, 81% of the patients with severe ophthalmopathy had hyperthyroidism(7). The date of the first eye manifestation in this report was symmetrically distributed within 18 months before or after the time of the diagnosis of hyperthyroidism. In our cases, the most common time for the onset of *Graves'* ophthalmopathy was 0-12 months after the diagnosis of hyperthyroidism and for thyroid dermopathy 12-24 months after the diagnosis. In 34% of the patients, *Graves'* ophthal--mopathy was beyond the first year of hyperthyroid diagnosis as opposed to 66% for the onset of thyroid dermopathy. It appears that in *Graves' disease* the time of the onset of thyroid dermopathy is later than opthalmopathy and its peak onset time is in the second year after the diagnosis of hyperthyroidism.

In terms of severity of ophthalmopathy in patients who have thyroid dermopathy, it seems that the majority have a significant proptosis and in 30% the ophthalmopathy is severe enough to require decompression surgery. However, for the patients referred to Mayo Clinic, there may be a referral bias. Cases with severe eye disease may be referred to the Mayo Clinic in order the decompressive surgery be done for them. However, Mayo Clinic data(8) indicate that in patients requiring decompression surgery, although the patients with dermopathy have a slightly higher degree of proptosis, the difference is not statistically significant. The degree of proptosis recurrence after decompression surgery and also the improvement of other parameters are not any different from the patients without dermopathy.

Although dermopathy indicates almost certain eye disease and usually relatively severe eye disease, it does not predict refractory response to therapy.

The available follow up of 120 patients of our series shows that there is at least 10% remission in a long follow up period. However, this under-represents the remission rate since most likely some patients who remitted might have not returned for follow up.

A true remission rate will be only known if all the patients are reexamined or information is obtained through a questionnaire. The observed partial remission was higher in the group that had local steroid.

We believe that the results of remission and partial remission have to be cautiously interpreted.

Table 1. Clinical characteristics of 150 patients with thyroid dermopathy

Variables	No. of patients	Relative frequency (%)
Palpable thyroid	106	70.6
Ophthalmopathy	149	99.3
Acropachy	11	7.3
Thyroid function*		
Hyperthyroid	23	15.3
Hypothyroid	11	7.0
Euthyroid	110	73.0
Clinical forms		
Non-pitting edema	76	50
Nodular	26	17.0
Plaque	28	18.0
Polypoid	1	0.7
Elephantiatic	1	0.7

* At the time of Mayo Clinic evaluation

Table 2. Types of therapy employed in 150 patients with *Graves' disease* associated with thyroid dermopathy

Modes of therapy	No. of patients	%
Thyroidectomy	12	8
I-131 therapy	105	70
Need for second I-131	32	21
Oral anti-thyroid only	8	5
Thyroidectomy+I-131 therapy	11	7

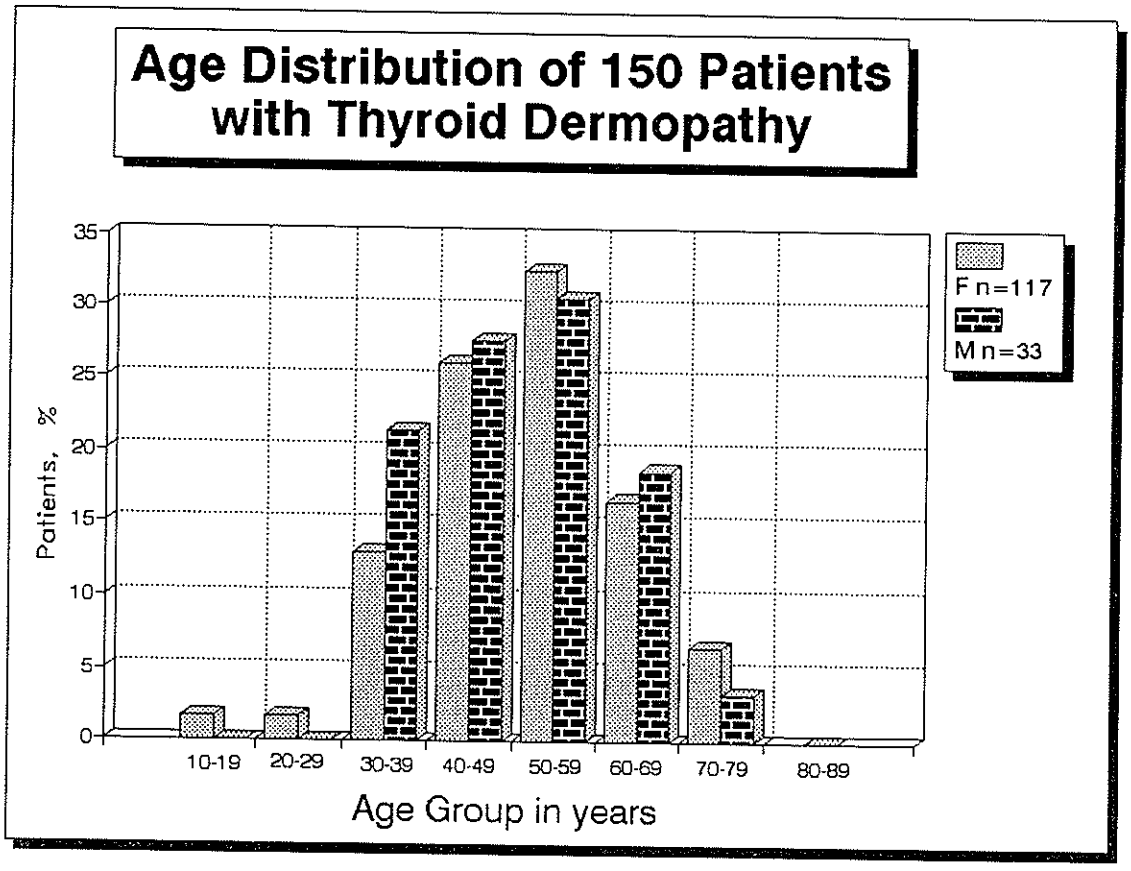

Fig. 1

Table 3. Characteristics of eye disease in 150 patients with thyroid dermopathy

Variables	No. of patients	%
Ophthalmopathy	149	99.3
Propotosis*(Krahn>20 mm)	132	88.0
Diplopia	62	41.6
Decreased visual acuity	42	28.7
Scotoma	18	15.0
Papilledema	4	2.6
Exposure keratitis	12	8.0
Need for systemic steroids	26	17.4
Decompressive surgery*	45	30.2

* Bilateral: 73%
Unilateral: 27%

Table 4. Proptosis in 149 patients with thyroid dermopathy and ophthalmopathy

	(Krahn exophthalmometer reading, mm) Mean ± S.D.		
	Right eye	Left eye	Significance
All patients	22.2 ± 1.5	22.6 ± 9	N.S*
Males	22.6 ± 2.1	22.8 ± 3.3	N.S*
Females	21.7 ± 1.2	21.7 ± 1.4	N.S.*

* N.S. = Not significant (p> 0.1)

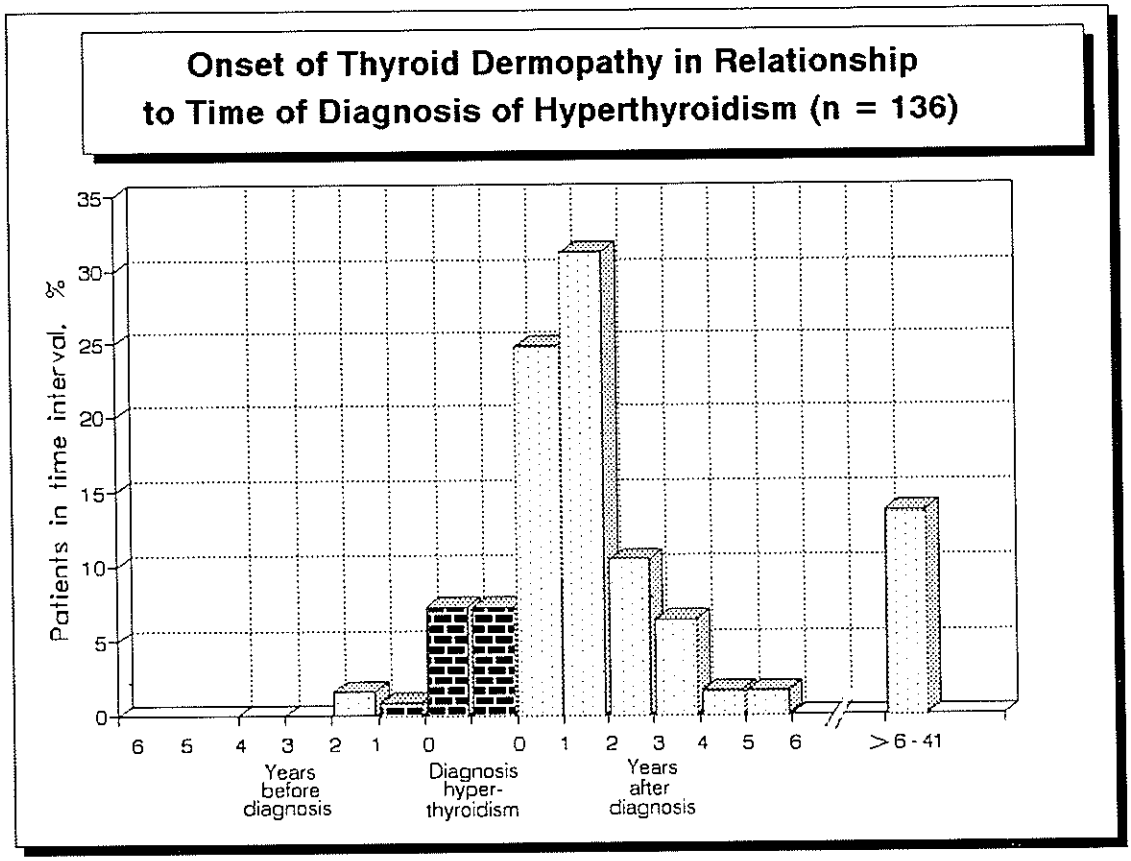

Fig. 2

Table 5. Features of ophthalmopathy in patients with thyroid dermopathy who had orbital decompression

	Decompressive surgery (n= 30)	**No decompressive surgery (n= 120)**
Proptosis (Krahn, mm) Mean ± S.D.	26.7±1.8	20.1±1.9*
Exposure keratitis	33%	1.6%*
Diplopia	93%	17.5%*
Decreased visual acuity	83%	14.0%*
Papilledema	13%	0.0%*

* All differences between the two groups are significant ($p < 0.05$).

Table 6. Manifestations of *Graves'* ophthalmopathy in different forms of thyroid dermopathy

Subtypes of dermopathy	**Proptosis (Krahn exophthalmometer** reading,mm) Mean±SD	**Diplopia** %	**Impaired vision** %	**Need for steroids or** decompression	**Exposure keratitis** %
Nodular* (n=26)	21.55 ± 3.08	50	19	19	0
Non-pitting (n=76)	19.36 ± 4.8	55	32	32	15
Plaque*	22.92 ± 4.24	46	7	7	0

* Statistical significance was achieved for the higher degree of proptosis in plaque and nodular forms of thyroid dermopathy.

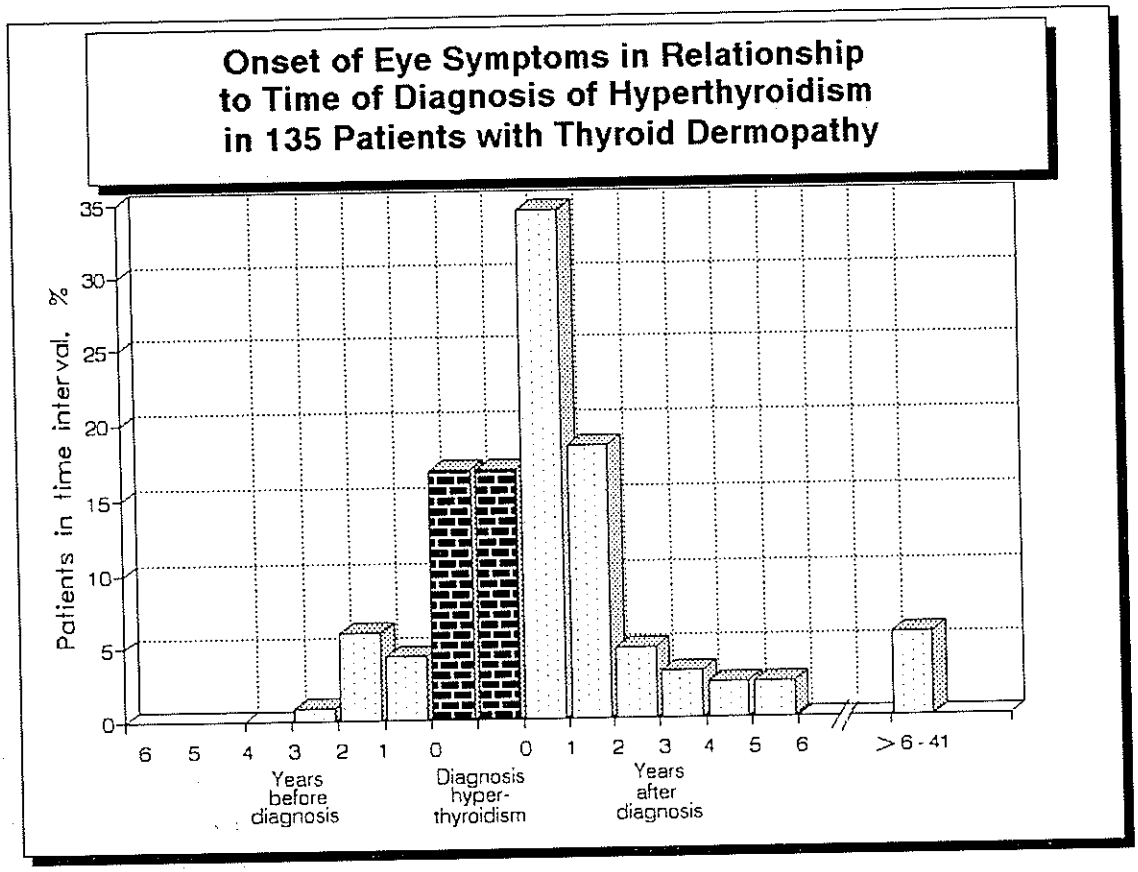

Fig. 3

Table 7. Documented remission in 120 patients with thyroid dermopathy 7±2.6 years (Mean ± S.D.), range of 19 years

	No. of patients	%
Complete remission	12	10
Partial remission	37	30

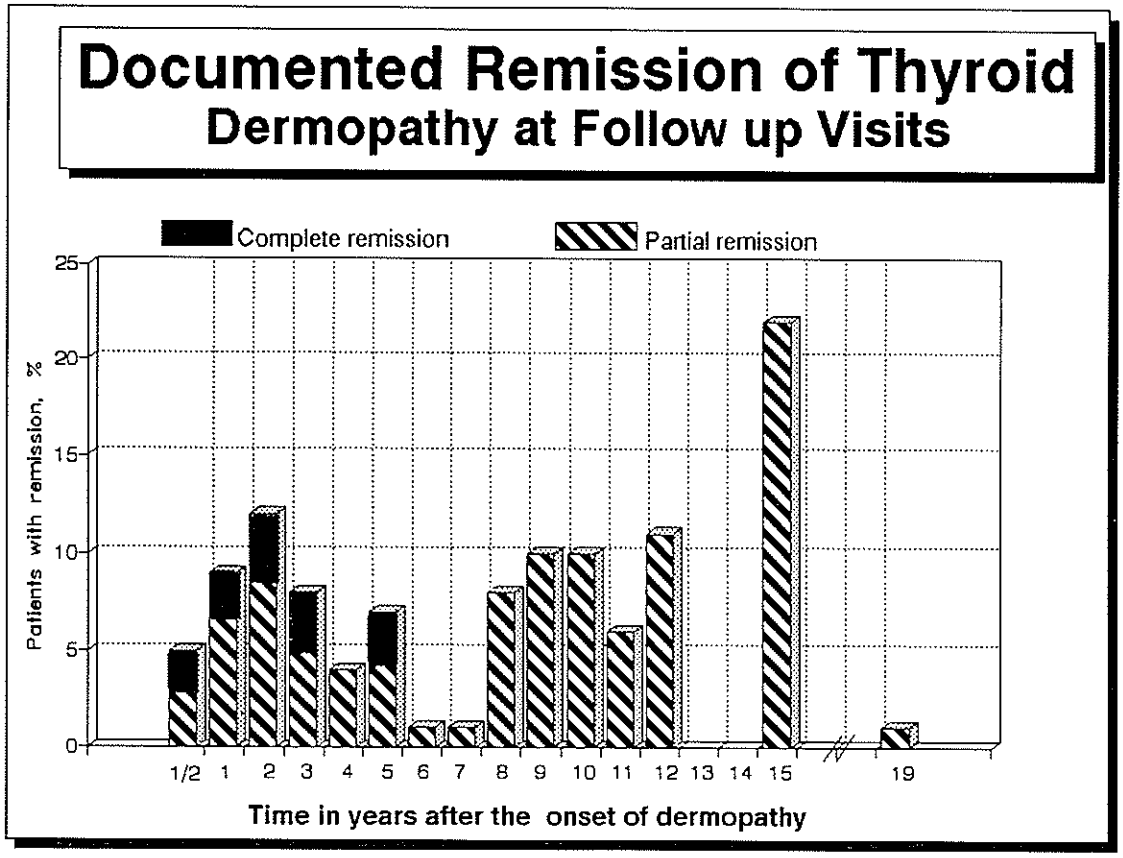

Fig. 4

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