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MINI REVIEW

Multiple Eruptive Dermatofibromas: A Review of the Literature

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In this review we summarize the characteristic features of multiple eruptive dermatofibromas based on an analysis of cases in the literature. Many researchers have reported multiple eruptive dermatofibromas diagnosed using the definition of "multiple" as the presence of at least 15 lesions. However, this criterion is arbitrarily chosen and might not be entirely valid for all cases. A more precise definition may include the eruption of several multiple eruptive dermatofibromas reported within a short period of time. Because more than half of the patients with multiple eruptive dermatofibromas have underlying diseases, and more than 80% of the underlying diseases are immune-mediated, multiple eruptive dermatofibromas could possibly be considered as a partial manifestation of an immune-mediated disease. This underscores the possibility of early diagnosis of immune-mediated diseases in patients with multiple eruptive dermatofibromas. ***Key words: underlying diseases; immune diseases; SLE; HIV.***

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Dermatofibroma (DF) is a common, benign fibrohistiocytic tumor that usually occurs on the legs. Cases of solitary DF or occasionally a few DFs are common, but multiple eruptive dermatofibromas (MEDF) are rarely observed (1–34). Multiple dermatofibromas were present in 106 of the 379 patients (28%) reviewed by Niemi (35): 76 patients (20%) had two lesions, 29 patients (8%) had between 3 and 10 lesions, and only one patient (0.3%) had more than 10 lesions.

In this review we summarize the cases of MEDF showing at least 3 DFs published in the English literature since 1960, and describe the characteristic features of this condition. Because of the widely accepted view that histiocytoma is a synonym of DF (5), we used both terms when retrieving cases from the literature.

Body distribution of multiple eruptive dermatofibromas

MEDF characteristically occur in the legs, as indicated in Table I, as do most DFs (19), regardless of the presence or absence of underlying disease. In contrast to ordinary DFs, however, they also occur in other parts of the body, where the number of lesions is larger. Facial lesions are extremely rare, as is also true of cases of ordinary DF. In some cases, MEDF occurred in unusual areas such as the palms and soles (7), eyelids (9) or buttocks (19) but, remarkably, none of these cases had any associated underlying disease. In general, MEDF arranged in a more limited area may not be associated with any underlying diseases.

Onset of multiple eruptive dermatofibromas

A typical clinical feature of MEDF is the sudden appearance of many DFs not only on the legs but also elsewhere on the body. In addition to the number of DFs, it is important to note the dynamic changes in some lesions within a short period of time in contrast to the static state usually observed in common DFs. Ammirati et al. (29) proposed that MEDF should be defined as the presence of 5 to 8 DFs appearing within a period of 4 months.

Definition of "multiple"

Since MEDF were first reported by Baraf & Shapiro in 1970 (3), defining "multiple"as the presence of at least 15 lesions, many researchers have reported cases of MEDF diagnosed on this basis (4, 14, 15, 18, 25, 31, 32). However, the relevance of the number 15 is still in question (4, 31). Out of the 39 case reports in which the number of lesions was specified in the literature, 20 (51%) had 15 or more DFs. However, even in those patients with 14 or fewer DFs, new DFs could have been in the process of proliferation. Conversely, DFs may also disappear spontaneously (15, 22, 31), as has occasionally been reported. Therefore, the definition of MEDF based purely on the number of DFs may not be entirely valid (21, 27). Defining MEDF solely on the basis of the number of lesions may be as arbitrary as defining the so-called sign of Leser-Trélat solely by the number of seborrheic keratoses.

Characteristic underlying diseases associated with MEDF

There are several reports indicating that patients with MEDF often have various underlying diseases. From our review, as presented in Table I, we deduce that the incidence of MEDF is higher among patients with underlying diseases (28/50, 56%) than among otherwise

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Table I. *A review of the patients with multiple eruptive dermatofibromas*

		Associated condition		Dermatofibromas	
Ref. No.	Sex/Age	Disease	Drug[a]	No.	Location[b]
1	F/71	Hydronephrosis	–	Over 30	LL
2	F/53	–	–	85	T, UL, LL
2	M/58	–	–	2000	T, UL, LL
2	F/38	–	–	> 1000	F, T, UL, LL
3	F/39	–	–	61	T, UL, LL
4	F/54	–	–	90	T, UL, LL
4	F/40	–	–	16	T, UL, LL
4	M/50	–	–	23	T, UL, LL
4	F/64	–	–	12	UL, LL
5	F/31	SLE	Steroid, Aza	15	UL, LL
5	F/19	SLE	Steroid	Several	T, LL
6	M/44	–	–	ND	T, LL
7	M/12	–	–	9	Palm
7	M/8	–	–	Multiple	Hand
7	F/36	–	–	Multiple	Palm
7	F/9	–	–	6	Palm, sole
8	F/49	SLE	ND	Multiple	LL
9	F/62	–	–	Multiple	Eyelid
10	M/52	–	–	ND	F, T, UL, LL
11	F/37	SLE	Steroid	6	T, UL, LL
12	M/47	–	–	10	T, UL, LL
13	M/27	–	–	> 100	T, UU, LL
14	M/53	Myasthenia gravis	Steroid, Cyc	50–70	T, UL, LL
15	F/41	SLE, Sjögren syndrome	Steroid	120	T, UL, LL
15	F/50	SLE	ND	27	T, UL, LL
15	F/28	SLE	Steroid	18	UL, LL
16	M/37	–	–	ND	LL
17	M/29	Atopic dermatitis	Steroid (topical)	Many dozens	F, T, UL, LL
18	M/45	Pemphigus vulgaris	Steroid	23	LL
18	F/20	SLE	Steroid	4	T, LL
19	F/23	–	–	ND	Buttock
20	F/38	SLE	Steroid	20	UL, LL
21	F/25	Pregnancy	–	9	T, UL, LL
22	F/52	SLE	Steroid	13	T, UL
22	F/33	–	–	11	T, UL, LL22
22	F/46	SLE, Sjögren syndrome	Steroid, Cyc	10	ND
23	M/24	HIV, hepatitis B	DHIV, INFα	11	T, LL
24	M/37	HIV	DHIV	7	T, LL
25	F/33	SLE, HIV	Steroid, DHIV	15	T, UL, LL
26	M/24	HIV, psoriasis	DHIV, Steroid, UVB	8	T, UL, LL
27	F/43	Sarcoidosis	Steroid, ACTH	20	T, LL
28	M/38	HIV	ND	ND	UL, LL
29	M/36	HIV	DHIV	7	T, UL, LL
29	M/40	HIV	DHIV	8	UL, LL
29	M/38	HIV	DHIV	5	T, UL, LL
30	F/18	–	–	ND	T, UL, LL
31	F/51	Mycosis fungoides, interstitial pneumonia	PUVA, UVB, Steroid	14	LL
32	M/45	HIV	DHIV	Multiple	LL
33	M/13	–	–	ND	T, LL
34	F/48	SLE	Steroid	About 20	LL

[a]Aza: azathioprine; Cyc: cyclophosphamide; DHIV: drugs for HIV infection; ND: not described.
[b]F: face; T: trunk; UL: upper limb; LL: lower limb; SLE: systemic lupus erythematosus; ACTH: adrenocorticotrope hormone.

healthy persons (22/50, 44%). MEDF are usually associated with systemic lupus erythematosus (SLE) (13/28, 46%) or HIV infection (9/28, 32%), followed by other immune-mediated diseases, such as myasthenia gravis and pemphigus vulgaris. Although in some previous studies it is suggested that diabetes mellitus (1), obesity (4), hyperlipidemia (4), and hypertension (4) might also be frequently encountered in these patients, a correlation between MEDF and the presence of these diseases, which have high rates of prevalence in the general population, seems to be questionable.

According to our reassessment of published reports,

the male:female ratio of patients with MEDF is 0.72:1, indicating a slight female predominance. When these patients are classified in terms of the presence or absence of underlying diseases (n = 22), the male:female ratio is 0.83:1 in patients with no underlying disease (n = 28), whereas it is 0.65:1 in those who had underlying diseases. However, this may be because SLE accounted for about half of the cases with underlying diseases, and it is well known that SLE occurs predominantly in women.

Because MEDF were associated with other diseases in more than half of the reviewed cases, and more than 80% of the underlying diseases were immune mediated, MEDF could be considered in part as a manifestation of an immune-mediated disease. In recent years, the development of MEDF has been regarded as a dermal manifestation of HIV infection (32). In some cases, the onset of MEDF preceded the onset and diagnosis of the associated immune-mediated disease (8, 15, 23). This underscores the possibility of early diagnosis of immune-mediated diseases in patients recognized as having MEDF.

It is of particular interest to clarify whether the symptoms of MEDF show any changes along with aggravation of the underlying disease, or, in other words, whether changes in the symptoms of MEDF can predict changes in the severity of the underlying disease. Only two cases were reported in which the two conditions showed parallel aggravation in severity (8, 31). Usually, however, there seemed to be no correlation between the severity of the underlying disease and the symptoms of MEDF.

Some patients with immune-mediated diseases developed MEDF after intake of immunosuppressive drugs or after an increase in the dose of the medication, suggesting a causal relationship between the medication and the development of MEDF (5, 11, 14, 15, 23, 26). Based on this data, the possibility of the occurrence of immunomodulatory, drug-induced MEDF has been discussed. However, it should be noted that the commencement, or increase in the dose of medication is usually prompted by aggravation of the underlying disease, and that it is therefore impossible to determine whether the development of MEDF is induced by aggravation of the underlying disease or by the use of drugs.

Etiology of multiple eruptive dermatofibromas

The etiology of DF is unclear. It may represent a neoplastic process or a persistent inflammatory proliferation of fibroblasts secondary to trauma (such as an insect bite) (36). Recently, it was proposed that DF represents an abortive immunoreactive process mediated by dermal dendritic cells (37). According to this hypothesis, the development of MEDF can be triggered by the inhibition of down-regulatory T cells in immunodeficiency states. The increased incidence of MEDF in patients with immune-mediated diseases and the relationship with immunosuppressive treatment strongly suggest that immune mechanisms may play a role in the pathogenesis of DF.

Conclusion

For the diagnosis of MEDF, it is important to note the dynamic changes in the form of an outbreak of lesions within a short period of time.

MEDF may develop in patients with immune-mediated diseases. Hence, the possibility of an underlying immune-mediated disease should be borne in mind when encountering patients with MEDF.

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