A. 皮膚悪性腫瘍ガイドラインを読んだことがありますか。

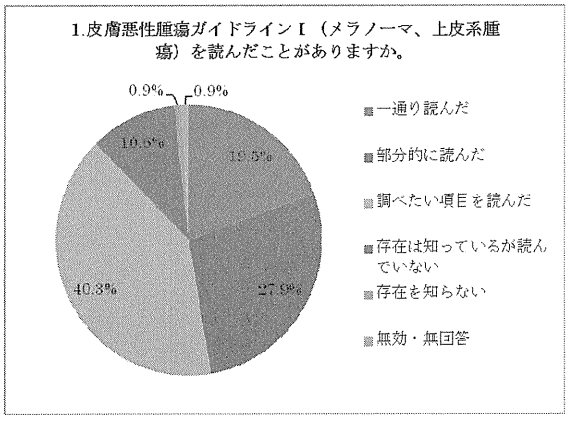

図１．皮膚悪性腫瘍ガイドラインⅠ（メラノーマ、上皮系腫瘍）を読んだことがありますか？

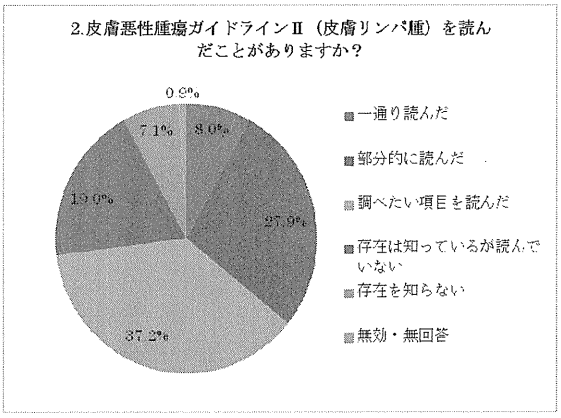

図２．皮膚悪性腫瘍ガイドラインⅡ（皮膚リンパ腫）をよんだことがありますか？

皮膚悪性腫瘍ガイドラインⅠ（メラノーマ、上皮系腫瘍）について

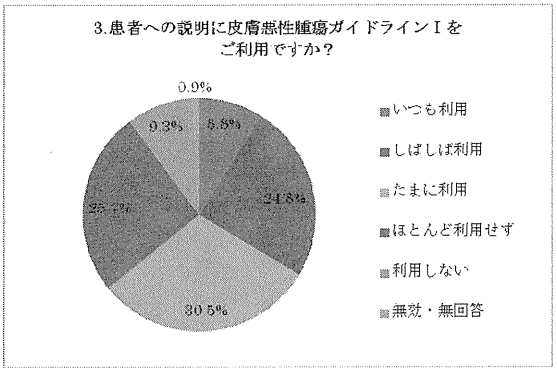

図３．患者への説明にガイドラインをご利用ですか？

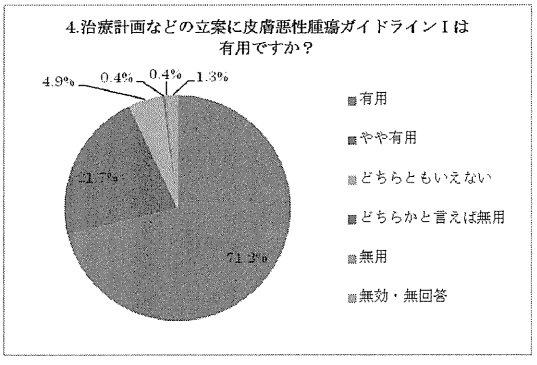

図４．治療計画などの立案にガイドラインは有用ですか？

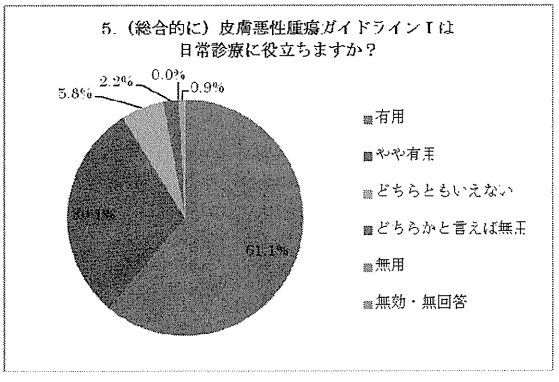

図５．（総合的に）ガイドラインは日常診療に役立ちますか？

皮膚悪性腫瘍ガイドラインⅡ（皮膚リンパ腫）について

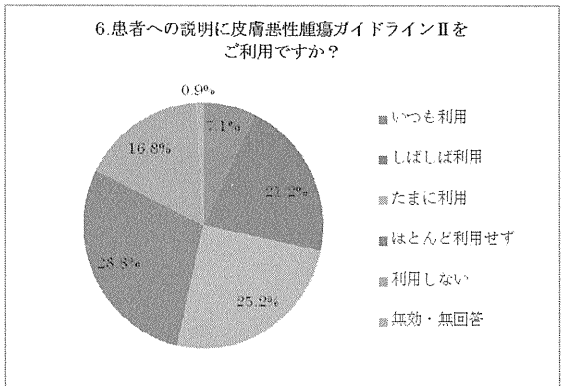

図６．患者への説明にガイドラインをご利用ですか？

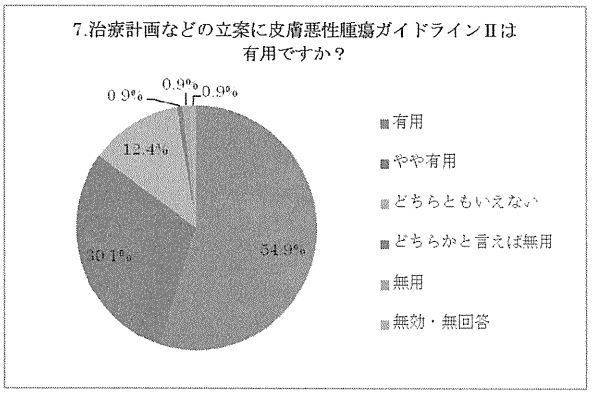

図７．治療計画などの立案にガイドラインは有用ですか？

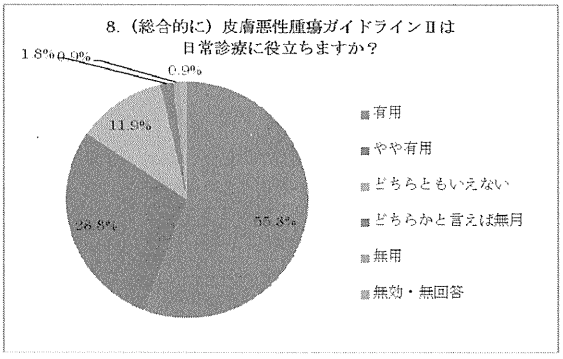

図８．（総合的に）ガイドラインは日常診療に役立ちますか？

皮膚悪性腫瘍ガイドラインの改訂・公開・関連セミナーについて

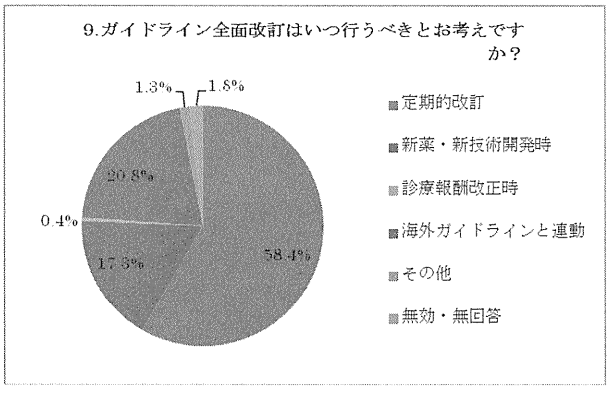

図９．ガイドライン全面改訂はいつ行うべきとお考えですか？

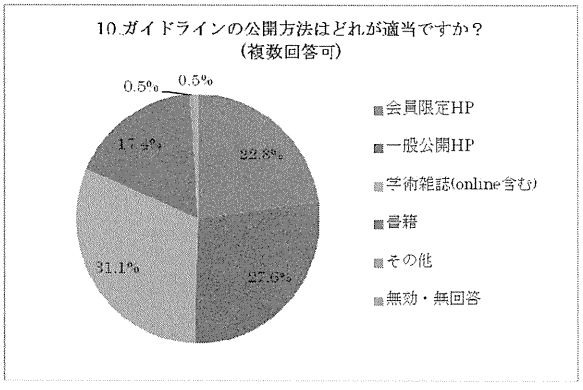

図10．ガイドラインの公開方法はどれが適当ですか？（複数回答可）

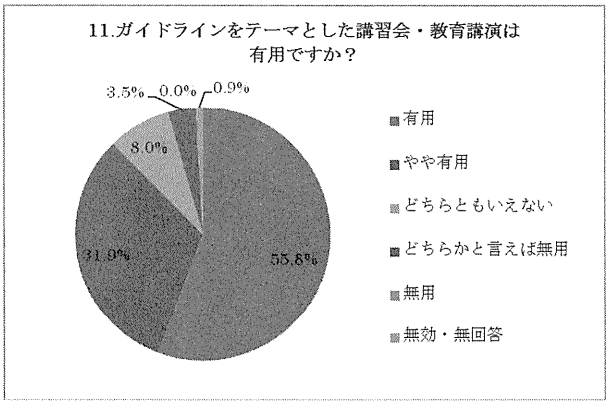

図 11．ガイドラインをテーマとした講習会・教育講演は有用ですか？

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Mark R. Pittelkow
Keiji Iwatsuki
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Skin Cancer — A World-Wide Perspective

Springer

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Preface

Dear reader

Is it still necessary to print a book?

Is it an anachronism to nowadays read print at all?

In the present era, the electronic equivalent of entire libraries of information is routinely distributed via the internet. This has led some to question the future relevance of print. However, it is our conviction that books still have their place in the world, and it is not merely because books preserve the information of generations with a security that electronic media cannot match. There is also great pleasure to be derived from lifting a text down from the shelf, repairing to a place of comfort, and wandering among pages of print thoughtfully collected and edited.

This book reviews the current state of the art among various aspects of skin cancer biology, diagnosis, and treatment. We have engaged five skin cancer experts as editors from five continents to collect information on the spectrum of cutaneous malignancies as it is described by the WHO classification. Furthermore, we have motivated the best researchers and clinicians to contribute their extensive knowledge base to the endeavor. This has resulted in the compilation of a unique reflection of medical and molecular knowledge about skin cancers. It is anticipated that this book will remain a basic reference for many years to come.

We invite you to take the time to go through this work.

In the name of all authors

Reinhard Dummer, MD
Mark R. Pittelkow, MD
Keiji Iwatsuki, MD
Adele Green, MD
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Histiocytoses

Keiji Iwatsuki

3.5

Core Messages

› Histiocytoses are a group of disorders encompassing reactive and neoplastic conditions derived from macrophages, dendritic cells, and histiocytes. The terminology and categorization of histiocytic disorders have been a controversial issue because of the vague definition of histiocytes. Recently, however, the cell lineage of myeloid-derived macrophages and dendritic cells is becoming clear through immunophenotypic analysis. The classification based on cell lineage provides us new insight into histiocytoses, although there are still some controversies between clinical and pathological entities. This chapter reviews the current definition, etiology, clinicopathologic features, and cell lineage of histiocytic disorders involving the skin, with special attention to the representative entities: Langerhans cell histiocytosis (LCH), Rosai–Dorfman disease, juvenile xanthogranuloma, and reticulohistiocytosis

3.5.1 Introduction

Histiocytoses are classified into two major categories: Langerhans cell histiocytosis (LCH) and non-LC histiocytosis (non-LCH). The latter may include the xanthogranuloma family and other histiocytic disorders. In 1987, the Histiocyte Society proposed a classification of histiocytic syndromes: (1) class I histiocytosis (LCH), (2) class II histiocytosis (non-LCH), and (3) class III histiocytosis (malignant histiocytosis) [17]. Recently, the revised classification of histiocytic disorders, including hematological disorders, was proposed based on cell lineage and biological behaviors: (1) dendritic cell-related, (2) macrophage-related, and (3) malignant disorders [4, 11]. According to this immunophenotypic classification, the dendritic cell group may include both LCH and the juvenile xanthogranuloma family, in which the proliferative histiocytoid cells share dermal/interstitial dendritic cells markers such as factor XIII and fascin. In order to avoid controversy in classification, this chapter describes the representative histiocytic disorders involving the skin, using dermatological diagnoses (Table 3.5.1).

3.5.1.1 *Langerhans Cell Histiocytosis*

Synonyms: Histiocytosis X, Langerhans cell disease (LCD), class I histiocytosis (by Histiocyte Society), Letterer–Siwe disease (acute disseminated LCD), Hand–Schüller–Christian disease (chronic multifocal LCD), eosinophilic granuloma (chronic focal LCD), congenital self-healing reticulohistiocytosis (Hashimoto–Pritzker disease)

3.5.1.1.1 Definition

LCH is defined as a proliferative disorder of LC type dendritic cells characterized by expression of S100 protein, CD1a and Langerin (CD207), and by racquet-shaped Birbeck granules in the cytoplasm. LCH may include four clinical subtypes previously used: (1) Letterer–Siwe disease for the acute, disseminated, or visceral LCH, (2) Hand–Schüller–Christian disease for the chronic but progressive, multifocal form, (3) eosinophilic granuloma for chronic, localized LCH, and (4) Hashimoto–Pritzker disease for the benign, self-healing variant. Langerhans cell sarcoma, or malignant LCH is a rare, high-grade malignant neoplasm with a LC-like phenotype and overt nuclear pleomorphism.

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Table 3.5.1 Histiocytic disorders involving the skin [3, 4, 7, 9, 11, 17]

Langerhans cell histiocytosis (LCH)	Class I histiocytosis
Non-LC histiocytosis (non-LCH)	Class II histiocytosis
Xanthogranuloma family	
Juvenile xanthogranuloma	
Generalized eruptive histiocytosis	
Benign cephalic histiocytosis	Dendritic cell-related
Erdheim–Chester disease	
Papular xanthoma	
Xanthoma disseminatum	
Necrobiotic xanthogranuloma	
Solitary reticulohistiocytoma?	
Sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease)	Macrophage-related
Multicentric reticulohistiocytosis (MCRH)	
Unusual variants	
Indeterminate cell histiocytosis	
Progressive nodular histiocytosis	
Hereditary progressive mucinous histiocytosis	
Sea-blue histiocytic syndrome	
Malignant histiocytosis	Class III histiocytosis
LC sarcoma	
Others (dendritic cell, macrophage-related)	

3.5.1.1.2 Etiology

A clonal proliferation of LC type dendritic cells has been demonstrated by X-linked polymorphic DNA probes including HUMARA [16]. In contrast, primary pulmonary LCH arising in cigarette smokers might be both clonal and non-clonal [18] and may have allelic loss of tumor suppressor genes [13]. Bombesin-like peptides in cigarettes may stimulate alveolar macrophages, leading to the proliferation of Langerhans cells [14]. A subset of LCH is hereditary, especially in monozygotic twins [1].

3.5.1.1.3 Clinical Manifestations

LCH shows a broad spectrum of symptoms, severity, organ involvement, and prognosis. The localized form of LCH, formerly designated as eosinophilic granuloma commonly occurs in the bones and skin, and lymph node or lung involvement is occasionally seen. The clinical course is usually indolent, and spontaneous regression may occur.

Hashimoto–Pritzker disease has been designated as congenital self-healing reticulohistiocytosis, because the lesions are usually present at birth and composed of a few to several nodules or multiple, disseminated cutaneous papules. Spontaneous clearance occurs by 2–3 months of age.

Hand–Schüller–Christian disease is a subtype of LCH characterized by multiple cutaneous lesions associated with systemic symptoms such as diabetes insipidus, exophthalmos, and multiple osteolytic lesions, although other visceral organs and lymph nodes may be affected. The disease is usually progressive, and needs systemic treatments.

Letterer–Siwe disease is the most aggressive form of LCH associated with multisystem involvement. Lesions on the skin and mucosa consist of multiple, disseminated papules, coalescent plaques, and ulcerative nodules (Fig. 3.5.1a, b). Hemorrhagic papules and vesicles may occur in aggressive cases. Systemic symptoms include fever, lymphadenopathy, anemia, thrombocytopenia, hepatosplenomegaly, pulmonary infiltration, and hemophagocytic syndrome.

3.5.1.1.4 Histopathology

LCH cells have a characteristic lobulated, folded, or kidney-shaped nucleus and consistently express S100 protein, CD1a, and Langerin (CD207) (Fig. 3.5.1c, d; Table 3.5.2). Ultrastructually, tennis racquet-shaped Birbeck granules are observed in cytoplasm and very rarely in the nucleus (Fig. 3.5.1e, f). Three histologic reactions have been reported in LCH: proliferative, granulomatous and xanthomatous type. The proliferative type presents with acute, disseminated papules, in which LCH cells are infiltrating beneath or within the epidermis, associated with T-cell infiltration (Fig. 3.5.1d). The granulomatous type is usually associated with the chronic stage of the disease and composed of multinucleated giant cells, eosinophils, and other cell types. The xanthomatous type may be seen in the bone lesions of Hand–Schüller–Christian type LCH with foam cells, eosinophils, and other reactive cells, the feature of which is similar to xanthogranuloma. In Hashimoto–Pritzker disease, the infiltrate is composed of LCH cells with abundant cytoplasm and giant cells showing a "ground glass" appearance.

3.5.1.1.5 Differential Diagnosis

Letterer–Siwe type LCH should be differentiated clinically from seborrheic dermatitis, Darier's disease, pityriasis lichenoides, prurigo, and non-LC histiocytoses. Some cases of Hashimoto–Pritzker disease may be confused with blueberry muffin baby. Immunological phenotyping differentiates LCH from other non-LCH and class II histiocytosis (by Histiocyte Society) by expressing CD68 but not CD1a or Langerin (CD207).

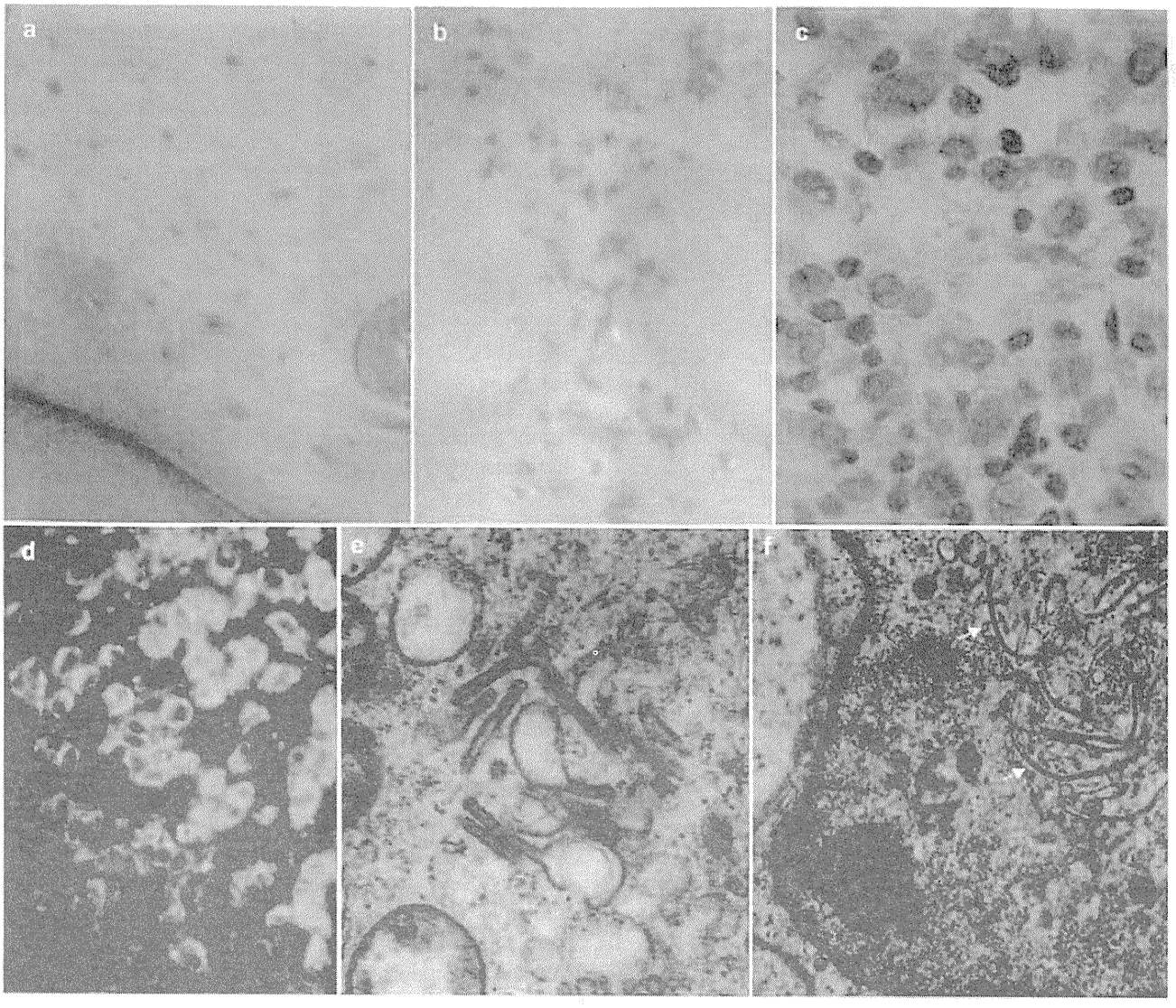

Fig. 3.5.1 Langerhans cell histiocytosis (LCH): Discrete, reddish or purpuric papules on the abdomen of an infant (**a**), and grouping, reddish papules on the anterior chest of an elderly individual, mimicking Darier's disease (**b**). Histiocytoid cells with a bilobulated nucleus express Langerin (CD207) (**c**). LCH cells expressing CD1a (*green*) and CD3-positive T lymphocytes (**d**). Racquet-shaped Birbeck granules in the cytoplasm (**e**) and very rarely in the nucleus (**f**; *arrows*)

3.5.1.1.6 Therapy and Prognosis

See Chap. 4.4

3.5.1.2 Indeterminate Cell Histiocytosis

Synonyms: Indeterminate dendritic cell tumor

3.5.1.2.1 Definition

A group of histiocytic lesions composed of possible indeterminate dendritic cells expressing S100 proteins and CD1a without Langerin (CD207) or Birbeck granules [10] and not consistent with other histiocitoses.

3.5.1.2.2 Etiology

Indeterminate cell histiocytosis can occur de novo or in association with a B-cell lymphoma, possibly as a result of B-cell dedifferentiation [7].

3.5.1.2.3 Clinical Features

Patients with indeterminate cell histiocytosis have a wide age range, from infants to the elderly, and may present with a

Table 3.5.2 Immunophenotypes of LCH cells and related cell lineage [4, 7, 11]

	Immunophenotype						
	S100	CD1a	Langerin	XIIIa	Fascin	CD68	MHC II
LCH	+	+	+	−	−	±	+cytoplasm
Interdigitating DC	+	+	−	−	+	±	+surface
Dermal/interstitial DC	±	−	−	+	+	+	±
Indeterminate DC	+	+	−	−	−		
Rosai–Dorfman	+	−	−	−	−	+	
Xanthogranuloma cells	−	−	−	+	+	+	
Veil cell/migrating LC	+	+	±	−	−		
Macrophage	±	−	−	−	±	+	+

variety of cutaneous manifestations: one or a few nodules to multiple papulonodules mimicking LCH.

3.5.1.2.4 Histopathology

The lesion is composed of mononuclear cell infiltrate containing foam cells and giant cells. The infiltrating histiocytes are similar to LCH cells in phenotype except for the absence of Langerin (CD207) reactivity and Birbeck granules (Table 3.5.2) [1].

3.5.1.2.5 Differential Diagnosis

The diagnosis can be made possible by exclusion of LCH and other histiocytic diseases by immunophenotyping. Indeterminate cells should be distinguished from LCH cells, interdigitating cells, dermal/interstitial dendritic cells, and histiocytoid cells in Rosai–Dorfman disease. Patients with nodular scabies and pityriasis rosea may contain similar cell types. It is difficult to exclude the lesions composed of accumulation of veil cells/migrating LC (if present).

3.5.1.2.6 Treatment and Prognosis

No clear data available.

3.5.1.3 *Sinus Histiocytosis With Massive Lymphadenopathy (Rosai–Dorfman Disease)*

3.5.1.3.1 Definition

A benign nodal or extranodal disease characterized by infiltration of histiocytoid cells harboring mononuclear cells in the cytoplasm (emperipolesis) and an immunophenotype of CD68+, S100+ without CD1a and Langerin (CD207).

3.5.1.3.2 Etiology

Unknown. EB virus or HHV-6 infection has been postulated.

3.5.1.3.3 Clinical Features

Rosai–Dorfman disease primarily involves cervical lymph nodes and is frequently associated with cutaneous lesions [15]. Cervical lymphadenopathy presents with fever, elevated ESR, leukocytosis or leukopenia, and polyclonal hypergammaglobulinemia. Cutaneous Rosai–Dorfman disease without nodal involvement occurs less commonly. Brownish, indurated plaques and nodules may occur in the skin solely (Fig. 3.5.2a). Compared to patients with the systemic form, patients with the cutaneous form are older and most commonly women [2, 5].

3.5.1.3.4 Histopathology

The cutaneous lesion is composed of a mixture of infiltrates: lymphocytes, plasma cells, neutrophils, macrophages, and histiocytoid cells harboring lymphocytes in pale abundant cytoplasm (emperipolesis) (Fig. 3.5.2b, c). The histiocytoid cells are positive for CD68 and S100 protein (Fig. 3.5.2d) and negative for CD1a and Langerin (CD207).

3.5.1.3.5 Differential Diagnosis

The clinical differential diagnoses may include abscesses, scrofuloderma, lupus vulgaris, cutaneous lymphoma, and sarcoidosis. Histologically, foreign body granuloma, reticulohistiocytoma, xanthogranuloma, LCH, and Malakoplakia (Michaelis–Gutmann bodies) should be differentiated.

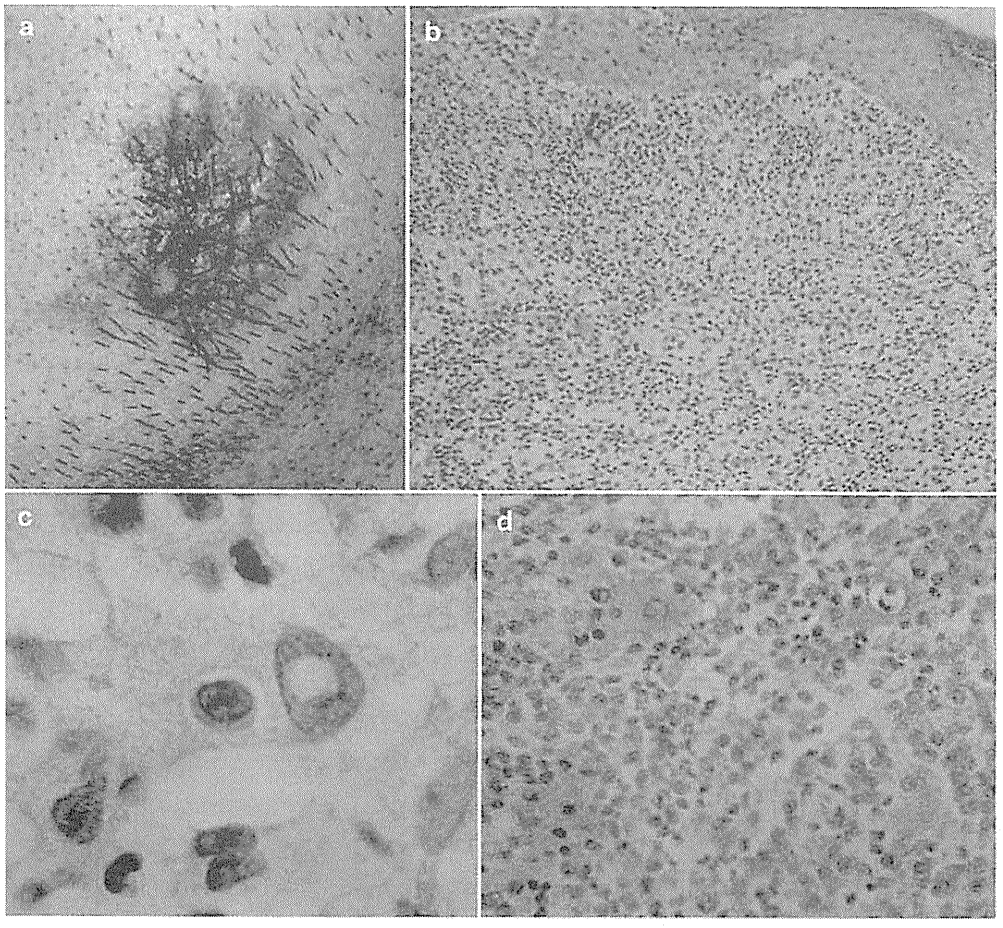

Fig. 3.5.2 Cutaneous Rosai–Dorfman disease: A reddish, indurated plaque with nodules (**a**) is composed of an admixture of histiocytoid cells, mononuclear cells, plasma cells and neutrophils (**b**). The histiocytoid cells contain lymphocytes in the cytoplasm (emperipolesis) (**c**), and express S100 protein (**d**). (Courtesy of Dr. N. Takiyoshi, Hirosaki University)

3.5.1.3.6 Treatment and Prognosis

Most cases with Rosai–Dorfman disease resolve spontaneously in months to years [2, 5, 15] but may recur in some cases. Surgical removal of the solitary skin lesion is an option for treatment.

3.5.1.4 Juvenile Xanthogranuloma

Synonyms: Xanthogranuloma (XG), non-X histiocytosis, class II histiocytosis (by Histiocyte Society)

3.5.1.4.1 Variants

Disseminated juvenile XG (JXG), deep JXG, generalized eruptive histiocytosis, benign cephalic histiocytosis, mononuclear xanthogranuloma, xanthoma disseminatum, papular xanthoma, scalloped cell xanthogranuloma, spindle cell xanthogranuloma, reticulohistiocytoma, Erdheim–Chester disease, necrobiotic xanthogranuloma.

3.5.1.4.2 Definition

A group of non-LCH (CD68+, CD1a–, Langerin–) associated with xanthomatous tissue reaction, but no clear consensus classification exists for this category. The infantile forms are usually benign and self-healing, with some cases presenting with organ involvement. The adult-onset, systemic diseases include Erdheim–Chester and necrobiotic XG.

3.5.1.4.3 Etiology

A triple association between JXG, NF-1 and myelomonocytic leukemia occurs [19], and LCH may also be associated [12]. The cell lineage of JXG has been postulated to be

dermal/interstitial dendritic cells because of the expression of factor XIII and fascin, but its specificity is still controversial (Table 3.5.2) [4, 11].

3.5.1.4.4 Clinical Features

The cutaneous lesions vary from one or several papules to numerous, disseminated papules and preferentially occur on the head, neck and trunk shortly after birth (Fig. 3.5.3a, b). No lipid abnormality is found. According to the Kiel Pediatric Tumor Registration [8], 34.5% of JXG were congenital, and 71.0% were diagnosed within the first year of life. Most cases of cutaneous JXG were solitary (81.0%), and 3.9% presented with visceral (systemic) involvement which may not be related to the dissemination of the cutaneous lesions. The early lesions are reddish and become brownish yellow because of the accumulation of foam cells. JXG with systemic involvement is rare, but significant morbidity and occasional deaths may occur. Of 34 children with systemic JXG [6], the extracutaneous site of disease was the subcutaneous soft tissue in 12 patients, central nervous system in 8 (Fig. 3.5.3c), liver/spleen in 8, lung in 6, and eye/orbit, oropharynx, and muscle in 4 patients each.

Solitary XG and reticulohistiocytoma are both self-limiting diseases that may occur in adults. Erdheim–Chester disease is an adult-onset, disseminated histiocytosis which predominantly affects the bones, lungs and kidneys, with a high mortality rate [3]. Necrobiotic XG may be associated with paraproteinemia or hematological malignancies such as plasma cell dyscrasia and multiple myeloma.

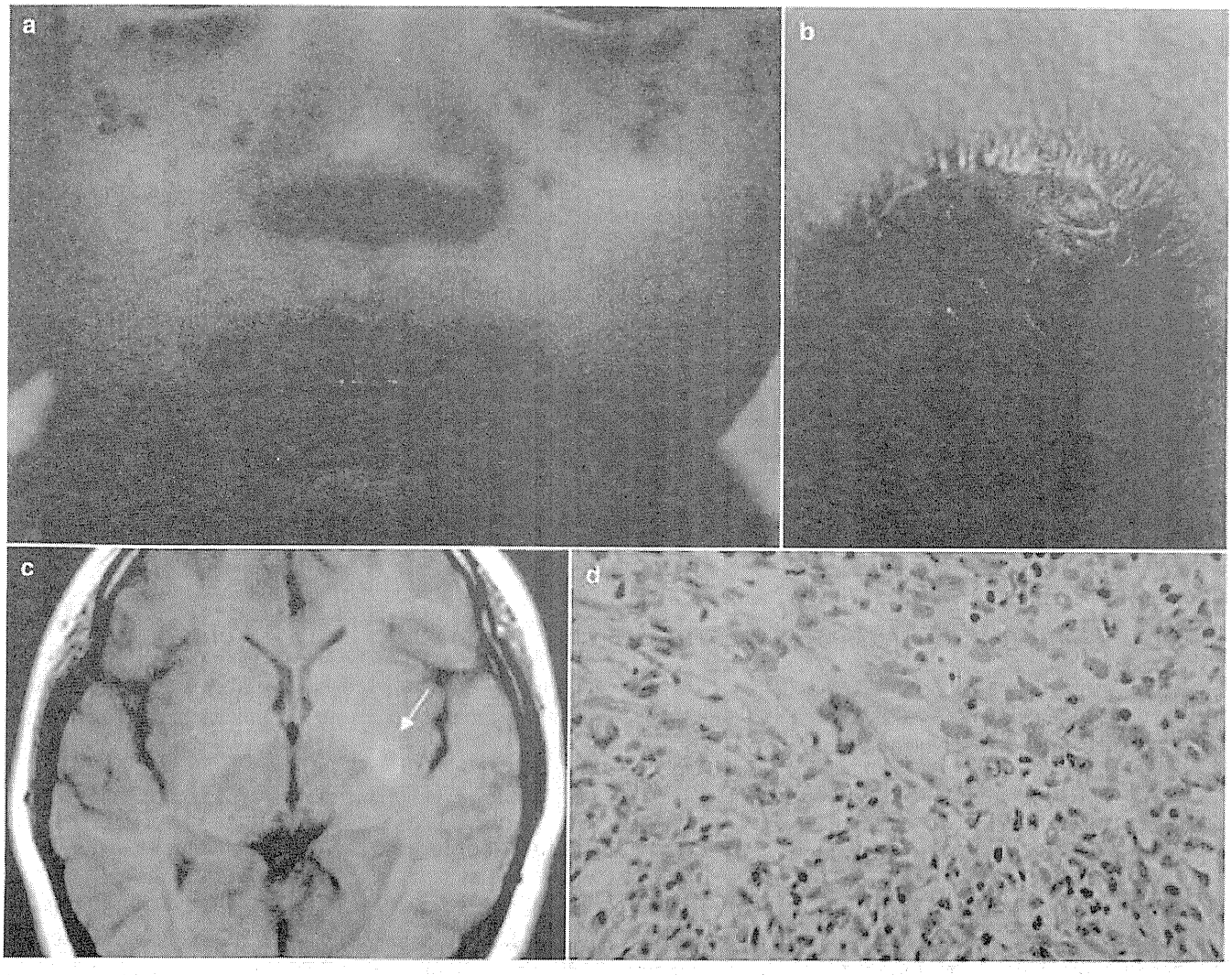

Fig. 3.5.3 Juvenile xanthogranuloma: Similarly-sized, reddish papules scattered on the face (**a**). A yellowish brown nodule on the chest in a 14 year-old girl (**b**) who presented with a solitary tumor in the brain (**c**; *arrow*). A mixed infiltrate of mononuclear cells, neutrophils and multinucleated giant cells containing lipid (**d**)

3.5.1.4.5 Histopathology

Infiltrates contain mononuclear cells and an admixture of other inflammatory cells such as lymphocytes and neutrophils (Fig. 3.5.3d). The early lesions are composed of mainly mononuclear cells, and the mature lesions contain a variable number of foam cells, characteristically Touton cells. Proliferating histiocytoid cells may express both macrophage and dermal/interstitial dendritic cell markers, including CD68, α1-antitrypsin, chymotrypsin, lysozyme, factor XIIIa, and fascin, and consistently negative for LCH markers such as S100 protein and CD1a (Table 3.5.2) [3, 4, 9, 11]. Based on these phenotypes, the JXG family has been classified as a group of dentritic cell tumors, but this has been a controversial issue. Solitary reticulohistiocytoma, a possible variant of XG, may contain many oncocytic macrophages and multinucleated histiocytes characterized by abundant, eosinophilic, finely granular cytoplasm, the feature of which is a so-called "ground glass" appearance.

3.5.1.4.6 Differential Diagnosis

Nodular JXG must be distinguished from Hashimoto–Pritzker disease, mastocytoma, and Spitz nevus. The multiple papules should be differentiated from LCH and early onset sarcoidosis. Patients with numerous papulonodules may be classified into the variants of JXG histopathologically, including xanthoma disseminatum, generalized eruptive histiocytosis, and benign cephalic histiocytosis.

3.5.1.4.7 Treatment and Prognosis

Both mucocutaneous lesions and organ involvement of JXG show spontaneous regression in most patients. Solitary or few lesions are successfully treated with excision. Patients with systemic JXG have been treated with radiation or systemic chemotherapy (see detail in Chap. 4.4).

3.5.1.5 Reticulohistiocytosis

3.5.1.5.1 Definition

Reticulohistiocytosis is divided into two categories: solitary reticulohistiocytoma and multicentric reticulohistiocytosis (MCRH). The solitary form, a possible variant of xanthogranuloma (see Chap. 3.4.1.4), generally occurs as a brownish yellow nodule on the head. MCRH is characterized by multiple, glossy, cutaneous lesions and is very frequently associated with fever, weight loss, and systemic symptoms such as symmetric erosive arthritis, various malignancies, and systemic inflammatory diseases [9].

3.5.1.5.2 Variant

Diffuse cutaneous reticulohistiocytosis (purely cutaneous from)

3.5.1.5.3 Etiology

Unknown, but immunologic responses to underlying autoimmune diseases or neoplasms have been postulated.

3.5.1.5.4 Clinical Features

MCRH preferentially occurs in females of the fifth or sixth decade, and presents with multiple, small papules or nodules on the extremities and face (Fig. 3.5.4a). Grouped papules around the periungal areas are called "coral beads." Oral or nasal mucosa may also be affected. Multiple papules and nodules on the mutilating fingers, due to erosive arthritis, suggest MCRH. Most patients with MCRH have polyarthritis, and some may have underlying disorders such as tuberculosis, hypothyroidism, diabetes mellitus, or internal malignancies, including carcinomas of cervix, ovary, breast, stomach and colon, melanoma, and hematological disorders [9].

3.5.1.5.5 Histopathology

The cutaneous lesion is composed of histiocytic infiltrates and multinucleated, eosinophilic giant cells with "ground glass" cytoplasm (Fig. 3.5.4b). The cells are positive for CD68 and negative for S100 protein, CD1a, and factor XIIIa. Similar histiocytoid cells are present in the synovium.

3.5.1.5.6 Differential Diagnosis

The differential diagnoses for MCRH are rheumatoid arthritis, sarcoidosis, Gottron's papules in dermatomyositis, and tophi.

3.5.1.5.7 Treatments and Prognosis

See Chap. 4.4

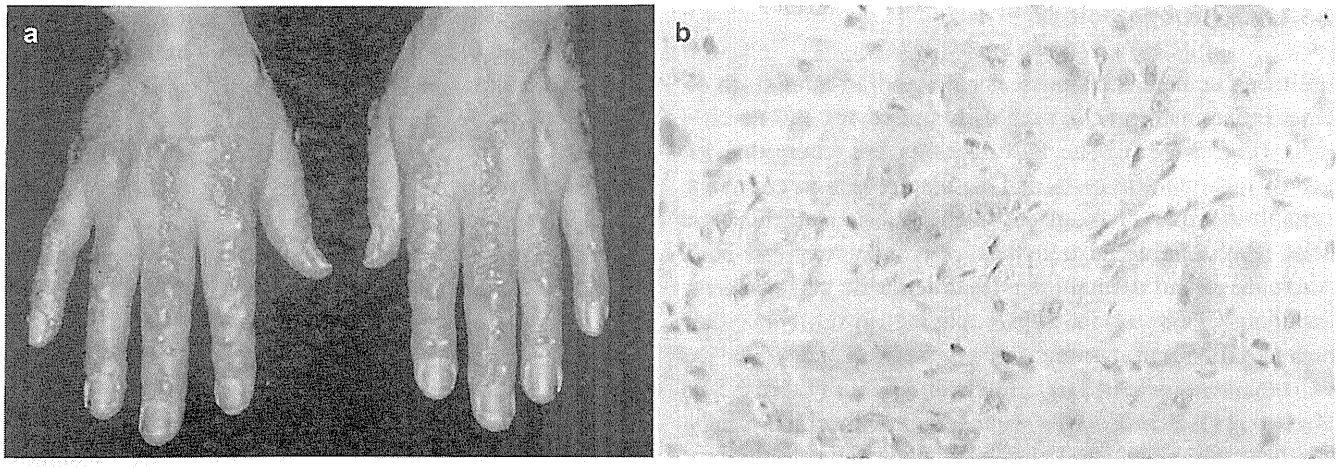

Fig. 3.5.4 Multicentric reticulohistiocytosis (MCRH): Skin-colored, glossy nodules on the dorsal surfaces of hands (a). Multinucleated giant cells with abundant, eosinophilic cytoplasm ("ground glass appearance") (b)

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Other Therapies 4.4

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4.4.1 Histiocytoses

Keiji Iwatsuki

4.4.1.1 *Langerhans Histiocytosis*

Prognostic factors for Langerhans cell histiocytosis (LCH) or class I histiocytosis may include: (1) the number of organs involved, (2) the severity of organ failure, and (3) the age of the patients. Complications such as hemophagocytic syndrome and thrombocytopenia also affect the prognosis [1–4]. In general, younger patients with widely disseminated disease and organ dysfunction have a high risk of mortality. In a series of 101 children with LCH [2], the overall survival rate was 79% at 1 year, 74% at 3 years, and 71% at 5 years; however, in patients with liver or spleen involvement, 1-year survival was 33% and 5-year survival was only 25%. In adult LCH [3], the probability of survival 5 years post diagnosis was 92.3% overall: 100% for patients with single-system disease, 87.8% for isolated pulmonary disease, and 91.7% for multisystem disease.

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4.4.1.1.1 Solitary LCH or Single-System Involvement

A localized or single-organ disease involving skin or bone usually shows a good prognosis and requires minimal treatment (Table 4.4.1) [1–4]. Watchful waiting may be the best choice for cases of solitary cutaneous LCH because of possible spontaneous regression. A solitary lytic lesion of the long bone (eosinophilic granuloma) is curable by curettage. Patients with LCH in the orbit or middle cranial fossa may present with diabetes insipidus and other endocrine abnormalities. Multiple cutaneous lesions have successfully been treated with topical steroid, topical nitrogen mustard [5], PUVA [6] (Fig. 4.4.1), and thalidomide [7]. In infants with Hashimoto-Pritzker disease, even though the lesions are multiple, observation may be the best option.

4.4.1.1.2 LCH with Multisystem Involvement

Infants with multisystem involvement have higher rates of mortality and morbidity. Corticosteroids have been effective initially, but recurrence is frequent. Monochemotherapy using vinblastine or etoposide is an option for therapy. Patients with multisystem involvement and organ dysfunction should be treated with polychemotherapy including corticosteroid, vincristine, cyclophosphamide, cytosine arabinoside, and methotrexate. Previous protocols designated DAL-HX [8], LCH-I [9], and JLSG-96 [10] as providing similarly beneficial therapeutic results. The LCH-III protocol is ongoing. Patients who respond to chemotherapy have an 88–91% survival rate, but for patients who do not demonstrate an early response, the survival rate drops to 17–34% [1]. Recent reports suggest that 2-chlorodeoxy-adenosine (2-CdA) appears to be useful in LCH treatment, but it cannot yet be recommended as first-line therapy [11].

4.4.1.2 *Non-Langerhans Cell Histiocytosis*

4.4.1.2.1 Juvenile Xanthogranuloma

Juvenile xanthogranuloma (JXG), a representative disorder of non-LC histiocytosis, is generally a benign, self-limiting

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histiocytic disorder of the skin, and requires no treatment. Both generalized eruptive histiocytosis and benign cephalic histiocytosis also disappear months to years after onset (Fig. 4.4.2). In the Kiel Pediatric Tumor Registry, cutaneous JXG showed a generally favorable prognosis with a low relapse rate (7.0%) and even complete involution after incomplete resection [12]. In contrast to the cutaneous form, systemic JXG with organ involvement and xanthoma disseminatum may be associated with significant complications requiring aggressive medical care, although visceral lesions may regress spontaneously. When feasible, surgical excision of the lesions may be curative. Disseminated, multisystem JXG needs LCH-based polychemotherapy including cytarabine, vincristine, methotrexate, and prednisolone [13, 14]. Therapeutic approaches should be decided while taking into account the risks and uncertain efficacy of anti-JXG therapy and the possibility of spontaneous regression of the disease [13].

Table 4.4.1 Therapy of choice for LCH and prognosis

Prognostic factors	
The number of organs involved, organ dysfunction	
Age (if multiorgan involvement exists)	
Response to the initial chemotherapy	
Complications (hemophagocytosis, thrombocytopenia)	
Single organ involvement	*(Therapy)*
Limited cutaneous	Observation, topical steroid, CO_2 laser topical nitrogen mustard [5], PUVA [6], thalidomide [7]
Localized bone	Curettage or excision, intralesional steroid, radiotherapy
Multiple	The same as above, systemic steroid, interferon α2 monochemotherapy (vinblastine, etoposide)
Multiorgan involvement	
No organ dysfunction	Monochemotherapy (vinblastine, etoposide) with or without systemic steroid
Organ dysfunction	Polychemotherapy (vincristine, doxorubicin, cyclophosphamide, chlorambucil) DAL-HX [8], JLSG-96 [9], LCH-III (ongoing)
Refractory case	2-chlorodeoxyadenosine [10]

4.4.1.2.2 Systemic and Progressive Forms of XG Family

This category may include progressive nodular histiocytosis (PNH), necrobiotic xanthogranuloma (NXH) and Erdheim-Chester disease. Patients with PNH may present with continuous development of new lesions but remain in good health without any treatment [15].

NXG is a chronic and progressive disease associated with systemic involvement such as thorax and granulomatous myocarditis. The prognosis is closely related to the underlying disorders including plasma cell dyscrasia, multiple myeloma and POEMS syndrome. Some cases were successfully treated with a low dose of chlorambucil, combination therapy of melphalan and prednisone, or methotrexate followed by corticosteroid [15].

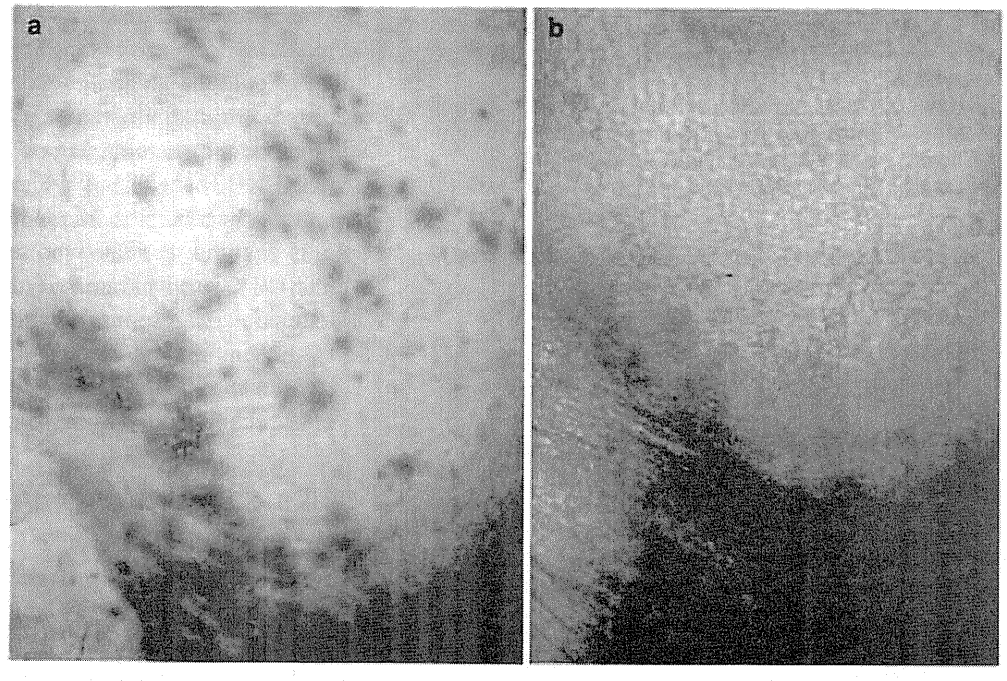

Fig. 4.4.1 PUVA treatment for adult LCH. Cutaneous manifestations before (a) and after (b) topical PUVA treatments [6]

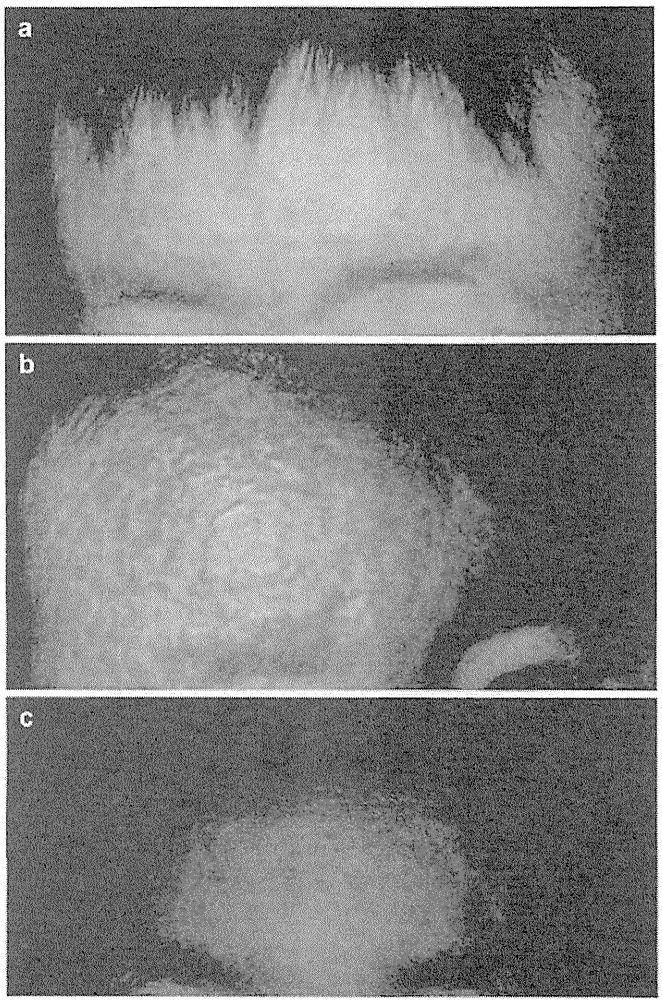

Fig. 4.4.2 Spontaneous regression of benign cephalic histiocytosis (BCH)/generalized eruptive histiocytosis (GEH). A 14-month-old boy had multiple reddish papules on the forehead mimicking BCH (**a**), which increased in number a month later, and expanded on the trunk symmetrically, the feature of which was consistent with GEH (**b**), and spontaneously regressed at the age of 4. During the clinical course, no apparent xanthomatous yellowish change was observed clinically

Erdheim-Chester disease has been treated with systemic steroids, radiation, LCH-based chemotherapy, interferon α and surgery, although the efficacy of these treatments has not fully been evaluated.

In the previous report, 22 (59%) of 37 patients died of the disease, and 8 (36%) died in less than 6 months [15, 16]. The mean survival duration was less than 3 years.

4.4.1.3 Multicentric Reticulohistiocytosis (MCRH)

Prior to treatment, underlying diseases such as tuberculosis, autoimmune diseases, and malignancies should be ruled out. Although nonsteroidal antiinflammatory drugs and corticosteroids have been used for arthritis, they do not improve the clinical course. There were some cases where polyarthritis was successfully treated with methotrexate, cyclophosphamide, chlorambucil, anti-TNF-α agents, and alendronate [17].

4.4.1.4 Rosai–Dorfman Disease

Spontaneous regression is common, but various treatments have been tried with some benefits: corticosteroids, thalidomide, liquid nitrogen, surgical excision, and radiotherapy [18].

Asian Skin and Skin Diseases

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Adult T-cell Leukemia/Lymphoma

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Summary

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell malignancy caused by human T-cell leukemia virus type 1 (HTLV-1). ATLL occurs in certain endemic areas of HTLV-1 infection, including Asia. The discovery of ATLL and HTLV-1 has not only contributed tremendously to the understanding of the pathogenesis of virus-induced neoplasms but also provided new insights into anthropology though retrovirus research. This review includes the clinicopathologic features of ATLL and the molecular pathogenesis induced by HTLV-1 infection.

Introduction

In 1976, Takatsuki and his colleagues reported, for the first time, an unusual peripheral mature T-cell leukemia which they designated adult T-cell leukemia (ATL). They reported that the majority of ATL patients were born in the Kyushu area, the southwestern part of Japan[1]. Miyoshi et al. established T-cell lines such as MT-1 and MT-2 from blood samples from ATL patients, using cocultivation with cord blood lymphocytes as a feeder[2]. Interestingly, chromosomal analysis demonstrated that some of the established T-cell lines were not derived from the ATL patients, but from the cord blood cells. Hinuma et al discovered the presence of serum antibodies directed against MT-1 cells in all ATL patients and some inhabitants in the Kyushu area, and postulated the involvement of a specific pathogen associated with ATL cells[3]. Although no viral particles were found in ATL cells *in vivo* by electron microscopy, virus-like particles were detected in the cell line cells. Using a molecular approach, Yoshida et al. clearly demonstrated that the virus-like particles were retroviruses containing reverse transcriptase activity, and that the T-cell lines harbored a proviral DNA sequence integrated in the host genome[4]. In addition to the common retrovirus structure of 'LTR-gag-pol-env-LTR', the newly isolated retrovirus, designated ATL virus (ATLV) in Japan, contained a unique pX sequence, resulting in a genome structure of 'LTR-gag-pol-env-pX-LTR'. Independent of the discovery of ATLV by Japanese researchers, Gallo and his colleagues isolated a retrovirus from a T-cell line, HUT102, established from a Caribbean patient with mycosis fungoides, who should actually have been diagnosed as having ATL in line with the present disease entity[5]. Retroviruses isolated from a Japanese group and an American group were later demonstrated to be essentially the same at the sequence level and designated as human T-cell leukemia virus type 1 or human T-cell lymphotropic virus type 1 (HTLV-1)[6].

Adult T-cell leukemia/lymphoma (ATLL), encompassing both leukemic and lymphomatous stages, is a peripheral T-cell malignancy caused by HTLV-1, but its infection alone is not sufficient to develop ATLL.

Epidemiology of ATLL

A sero-epidemiological survey by Tajima et al demonstrated that HTLV-1 infections are prevalent in Japanese,

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