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Relationship between histiocytosis and abnormal lymphoid differentiation. Case report and review of the literature.

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ABBREVIATIONS

5FU	5-fluorouracil
2-CDA	2-chlorodeoxyadenosine
AH	atypical histiocytosis
ALL	acute lymphoblastic leukemia
ARA-C	cytarabine
AWD	alive with disease
bp	base pairs
CDKN 2A	cyclin-dependent kinase inhibitor
CML	chronic myelogenous leukemia
CMP	cyclophosphamide
CNS	central nervous system
COALL	cooperative study group for childhood acute lymphoblastic leukemia
CR	complete response
CSA	cyclosporine
CT	computed tomography
DC	dendritic cells
DCP	dendritic cell proliferation
DN	double negative
DNA	deoxyribonucleic acid
DOD	dead of disease
DP	double positive
DX	dexamethasone
ELP	earliest lymphoid progenitor
FL	follicular lymphoma
GPOH	german society for pediatric oncology and hematology

IT	intrathecal
H&E	hematoxylin-and-eosin
HLH	hemophagocytic lymphohistiocytosis
H/DCS	histiocytic/dendritic cell sarcoma
HUMARA	human androgen receptor
IGMT	international ImMunoGeneTics system
IVIG	intravenous immunoglobulin
JCML	juvenile chronic myelogenous leukemia
JXG	juvenile xanthogranuloma
LCH	Langerhans cell histiocytosis
LKR	lymph node registry in Kiel
LV	leucovorin
MPDL	methylprednisolone
NA	not available
NED	no evidence of disease
NF-1	neurofibromatosis type 1
NHL	non-Hodgkin lymphoma
NLCH	non-Langerhans cell histiocytosis
NOTCH-1	Notch homolog 1
PAX 5	paired box protein 5
PCR	polymerase chain reaction
PDL	prednisolone
PDN	prednisone
T-ALL	acute lymphoblastic T-cell leukemia
TCR-γ	T-cell receptor gamma chain
THL	true histiocytic lymphoma

VBL	vinblastine
VCR	vincristine
VP16	etoposide

SUMMARY

Histiocytosis encompasses a heterogenous group of disorders which show a pathological accumulation and infiltration of monocytes, macrophages and dendritic cells in the affected tissue. They are relatively frequent in the pediatric population accounting for approximately 4-5,4 per 1000 000 population. Currently they are divided into Langerhans cell histiocytosis (LCH), non-Langerhans cell histiocytosis (NLCH) and malignant histiocytosis, according to the histologic findings and the clinical picture. Traditionally histiocytosis have been thought to derive from the myeloid lineage, however recent reports have found a clonal relationship of both LCH and malignant histiocytosis with lymphoid malignancies suggesting a lymphoid origin. It is currently not known if this phenomena extends to NLCH. In this thesis, we examine the question wether NLCH, in particular Juvenile xanthogranuloma (JXG), could also be related to the lymphoid lineage. We present evidence form the literature and form a unique case which shows a direct correlation between them.

JXG is the most frequent form of NLCH. It usually manifests itself as a benign, self limited tumour of the skin, that appears mostly during the first year of life. In some cases JXG can present as a systemic disease with considerable morbidity and mortality, particularly when the central nervous system is involved. We present a 5 year-old girl who suffered from an abnormally aggressive systemic JXG, which developed only 5 months after the diagnosis of cortical T-cell acute lymphoblastic leukemia (T-ALL). The JXG rapidly infiltrated lungs, liver, kidneys and gastrointestinal tract, leading to the patient's death. Examination of the T-cell receptor gamma (TCR-γ) rearrangement in T-ALL blasts, JXG infiltrated lymph node biopsies and micro-dissected JXG histiocytes revealed an identical bi-allelic TCR-γ rearrangement in all samples, thus providing evidence for a clonal relationship between T-ALL and JXG in the presented case. Even if it is difficult to make associations between tumor biology and normal lymphopoiesis, these findings suggest a common precursor cell for both diseases.

Analyzing the published cases of lymphoid malignancies related to histiocytosis, we found a grater number of case reports of B-cell related primary malignancies compared to T-cell related primary malignancies. We also found that the distribution of secondary malignancies between groups vary. The group of B-cell related primary malignancies had more cases of malignant histiocytosis (H/DC sarcoma) which appeared in a shorter time interval (median 0,5 years) compared to the group of T-cell related primary malignancies were the most frequent secondary malignancy was LCH and the interval between diseases was longer (medias 1,4 years). The age distribution between groups also differed. The group of T-cell related primary malignancies had a younger age of onset (average 6 years) compared to the group of B-cell related primary malignancies (average 42,8 years). The reduced number of case reports makes it difficult to draw conclusions. However, it appears that some forms of histiocytosis are related to the lymphoid lineage. Further work-up is needed to better understand this relationship and the pathogenesis of histiocytosis.

ZUSSAMENFASSUNG:

Histiozytosen umfassen eine heterogene Gruppe von Erkrankungen, die eine pathologische Akkumulation und Infiltration von Monozyten, Makrophagen und dendritischen Zellen im betroffenen Gewebe zeigen. Im Kindesalter haben sie eine Inzidenz von 4-5,4 pro 1 000 000. Aktuell werden Histiozytosen je nach histologischem Befund und klinischen Bild in Langerhans-Zell-Histiozytosen (LCH), Non-Langerhans-Zell-Histiozytosen (NLCH) und maligne Histiozytosen klassifiziert. Traditionell wurde angenommen, dass Histiozytosen von der myeloischen Zellreihe abstammen. Allerdings wurde vor wenigen Jahren eine klonale Verwandtschaft zwischen LCH, maligne Histiozytosen und sekundär auftretenden malignen Erkrankungen lymphatischen Ursprungs gefunden, die diese Hypothese widersprechen (Feldmann et al. 2004, 2005). Derzeit ist nicht bekannt, ob die Gruppe der NLHC auch eine Beziehung zu lymphatischen Zellreihen haben könnte. In dieser Dissertation untersuchen wir ob das juvenile Xanthogranulom (JXG), die häufigste Form der NLHC, auch mit einer sekundär auftretenden Erkrankung lymphatischen Ursprungs eine klonale Verwandtschaft haben kann. Wir führten eine systematische Literaturrecherche durch und präsentieren einen einzigartigen Fall, der eine direkte Korrelation zwischen beiden Krankheitsbildern zeigte.

Das JXG äußert sich meist als eine gutartige, begrenzte Neubildung der Haut, die in der Regel während des ersten Lebensjahres auftritt. In einigen Fällen kann sich das JXG als eine systemische Erkrankung mit erheblicher Morbidität und Mortalität manifestieren. In dieser Arbeit präsentieren wir den Fall eines 5 Jahre altes Mädchen, das eine ungewöhnlich aggressive Form eines systemischen JXG entwickelte. Die Diagnose des JXG wurde ca. 5 Monate nach der Diagnose einer kortikalen T-Zell akuter lymphatischer Leukämie (T-ALL) gestellt. Das JXG infiltrierte Lunge, Leber, Nieren und Gastrointestinaltrakt, und führte schließlich zum Tod der Patientin, 252 Tage nach Diagnose der T-ALL. Die Analyse von T-Zell-Rezeptor gamma (TCR-γ)-rearrangements in Proben von Blasten der T-ALL, JXG infiltrierten Lymphknoten und einzelnen Zellen des JXG, die durch mikordissektion gewonnen wurden, zeigten ein identisches biallelisches TCR-γ-rearrangment. Das identische biallelische TCR-γ-rearrangment bewies - im vorliegenden Fall - eine klonale Verwandschaft zwischen der T-ALL und dem JXG. Auch wenn es schwierig ist auf Zusammenhänge zwischen Tumorbiologie und normaler Lymphopoese zu schließen, deuten diese Ergebnisse auf eine gemeinsame Vorläuferzelle für beide Krankheiten hin.

Um eine bessere Übersicht über den Zusammenhang zwischen Histiozytosen und Erkrankungen lymphatischen Ursprungs zu haben, führten wir eine systematische Literatur-Recherche durch. Wir suchten in Pubmed von Januar 1970 bis Februar 2011 folgende Stichwörter: clonal relationship, histiocytosis, langerhans cell histiocytosis, non langerhans cell histiocytosis, malignant histiocytic disorder, leukemia, lymphoma, lymphoid origin, IgH, TCR rearrangment, hematologic malignancy, histiocytic sarcoma, juvenile xanthogranuloma, Rosai Dorfman. Wir fanden eine größere Anzahl an veröffentlichen Fällen von sekundär auftretenden Histiozytosen, die nach einer mit B-Zell-assoziierten Erkrankungen auftraten, im Vergleich zu sekundär auftretenden Histiozytosen, die mit Erkrankungen des T-Zellsystem assoziiert waren. Die Art der sekundären Histiozytosen zwischen beiden Gruppen waren ebenfalls unterschiedlich. Die Gruppe von B-Zell-assoziierten Erkrankungen hatte eine größere Anzahl an malignen Histiozytosen, die in einem kürzeren Zeitintervall (Medianwert 0,5 Jahre) erschienen. In der Gruppe von T-Zell-assoziierten Erkrankungen war die häufigste sekundäre Histiozytose die LCH und das Intervall zwischen den Erkrankungen war länger (Medianwert 1,4 Jahre). Die Altersverteilung zwischen den Gruppen war zudem unterschiedlich. Das durchschnittliche Alter bei Diagnose der Gruppe der T-Zell-assoziierten Erkrankungen war 6 Jahre im Vergleich zu der Gruppe der B-Zell-assoziierten Erkrankungen (im Durchschnitt 42,8 Jahre). Die geriinge Anzahl von Fallberichten macht es schwierig, Schlussfolgerungen zu ziehen. Es scheint jedoch, dass einige Formen der Histiozytosen lymphoider Abstammung sein können. Weitere Untersuchungen sind notwendig um diese Beziehung und die genauere Pathogenese der Histiozytosen besser zu verstehen.

1. INTRODUCTION

Histiocytosis encompasses a group of diverse disorders with a common primary event: the pathological accumulation of monocytes, macrophages and dendritic cells in the affected tissue [1]. The clinical presentations vary greatly, ranging from localized and mild, to disseminated and life threatening forms. More than a century after their first description the pathophysiology remains unclear and the treatment is frequently nonspecific, showing the need for an improved understanding of the etiology and pathogenesis of these disorders [2,3].

Recently there have been increasing reports of a genetic association between the lymphoid lineage and 2 groups of histiocytosis: Langerhans cell histiocytosis (LCH) and malignant histiocytosis [4-8]. However up to now, there have been only few associations between the lymphoid lineage and non-Langerhans cell histiocytosis (NLCH). The co-occurrence of T-ALL and a systemic form of JXG, in a patient treated at our hospital, gave us the opportunity to analyze relationship between them.

We performed a systematic literature research and present the case of a 5 year-old girl who suffered from an abnormally aggressive systemic JXG, which developed only 5 months after the diagnosis of cortical T-cell acute lymphoblastic leukemia (T-ALL).

1.1 Histiocytosis

Histiocytosis is defined as the abnormal proliferation of histiocytes. The term histiocyte was originally used to designate a large cell normally found in lymph nodes and spleen that was morphologically nonspecific, but had a voluminous, granulated cytoplasm, sometimes containing phagocytized particles [9]. The term histiocyte was later used to describe the fully differentiated end cells of the monocyte/macrophage lineage in the lung, and Kupffer cells in the liver [1,10]. More recently, the term has been extended to include another group of cells comprised of interdigitating dendritic cells of the lymph nodes, thymus and spleen, Langerhans cells of the skin, as well as dendritic reticulum cells. The term histiocyte, as currently used, includes cells of both the monocyte/macrophage series and the Langerhans/dendritic cell series [1]. (See table 1)

Table 1. Histiocytic cells, location and physiological function other than antigen presentation. Taken and adapted from [11-14].

Cell Type	Location	Function (other than antigen presentation)
Dendritic cells		
Peripheral blood dendritic cell	Peripheral blood	Migratory
Langerhans cell	Skin, epidermis, cervix, vagina, stomach, esophagus	Antigen uptake and processing transport to lymph nodes, Antigen transfer
Veiled cells	Afferent lymphatics	Antigen transfer
Interdigitating dendritic cell	Lymph node paracortex (T area), periarteriolar lymphatic sheath of the spleen	Antigen presentation
Thymic dendritic cell	Thymic medulla	Induction of immune tolerance
Interstitial dendritic cell	Parenchymal organs (excluding brain and central cornea)	Antigen uptake/processing?
Indeterminate cells of the skin (dermal dendrocytes)	Dermis	Antigen presentation
Follicular dendritic cell	Germinal center of lymph nodes	Maintenance of long-term immunologic memory
Monocytes/Macrophages		
Monocytes	Peripheral blood	migratory, homeostasis and inflammation
Kupfer cells	Liver	Phagocytosis and immunomodulation
Interstitial and alveolar macrophages	Lung	Phagocytosis and immunomodulation
Type A synoviocytes	Synovial membrane	Phagocytosis and immunomodulation
Osteoclast	Bone	Phagocytosis and immunomodulation
Microglial cells	Brain and Retina	Phagocytosis and immunomodulation
Multinucleated giant cells	Granulomas	Phagocytosis and immunomodulation
Tissue macrophage	Connective tissue, spleen, lymph nodes, bone marrow, intestinal wall, breast milk, placenta	Phagocytosis and immunomodulation

Consequently, histiocytosis encompasses the proliferation of cells derived from the monocyte/macrophage and Langerhans/dendritic cell series. While the exact ontogeny of these cells remains poorly understood, histiocytes currently are thought to arise from a common CD 34 positive progenitor within the bone marrow [15], which later evolves to a common myeloid precursor that later gives rise to Macrophages, Neutrophils and Langerhans and dendritic cells [16]. **(See Figure 1)** However, there are studies in mice that suggests that Langerhans cells might derive from lymphoid progenitors [17]. Also an increasing number of case reports show that the malignant counterpart of these cells often carry lymphoid genetic markers, as explained in detail later [7,8].

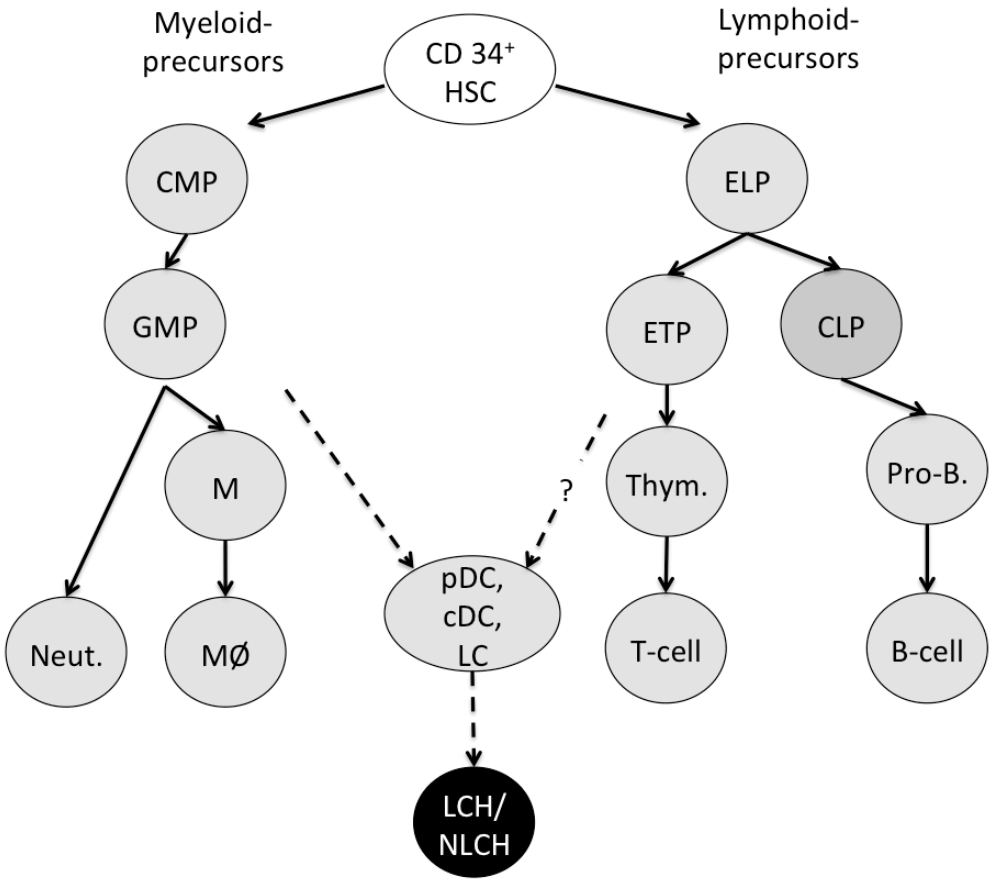

Figure 1. Hematopoiesis and normal DC development. RBC: red blood cells, CMP: common myeloid progenitor, GMP: granulocyte/macrophage progenitor, M: monocytes, Neut.: neutrophils, Mϕ: macrophages, HSC; hematopoietic stem cell, ELP: earliest lymphoid progenitor, ETP: early T-lineage progenitor, Thym. thymocytes, CLP: common lymphoid progenitor, Pro-B: Pro B cell, pDC: plasmacytoid dendritic cells, cDC: conventional dendritic cells, LC: Langerhans cells. LCH: Langerhans cell histiocytosis, NLCH: non-Langerhans cell histiocytosis. Taken and adapted form [16].

1.2 Classification

Few disease classifications are as confusing as the histiocytic disorders. At the time of the initial description, few reliable markers were available to determine the lineage or the stage of differentiation. Moreover, malignancy as applied to the histiocytic disease was an operational definition founded on an aggressive clinical course or aberrant morphology rather than on knowledge of clonality and altered cellular differentiation. These uncertainties stimulated a proliferation of multiple names for similar clinical syndromes [1,12].

The nomenclature used to describe histiocytic disorders has changed over time, reflecting the wide range of clinical manifestations and the variable clinical severities of these disorders [15]. With the advent of ultrastructural studies and immunohistochemical staining, the Histiocyte Society proposed reclassification of the histiocytosis based upon the predominant cell type within the infiltrate. The initial classification included Langerhans cell histiocytosis (Class 1), non-Langerhans cell histiocytosis (Class 2) and malignant histiocytosis (Class 3) [18,19]. More recently, a revised classification schema was published, dividing them into dendritic cell related disorders (Class 1): which include LCH, and JXG; macrophage-related disorders (Class 2): which include primary and secondary hemophagocytic syndromes, Rosai-Dorfman disease; and malignant histiocytic disorders (Class 3): which include monocyte-related leukemias and histiocytic/dendritic cell sarcoma (H/DC sarcoma) [15,19-21]. (**See table 2**) In clinical practice however, histiocytosis are still broadly grouped in Langerhans cell histiocytosis (LCH), Non-Langerhans cell histiocytosis and Malignant histiocytic disorders.

Table 2. Classification of Histiocytosis according to the Writing Group of the Histiocyte Society. Taken and adapted from [15, 19-21].

Class	Syndromes	Group
1. Dendritic-cell related	LCH	**LCH**
	JXG Solitary histiocytomas with a dendritic phenotype	**NLCH**
2. Macrophage related	Primary and secondary hemophagocytic syndromes. Rosai-Dorfman disease Solitary histiocytoma with a macrophage phenotype	
3. Malignant histiocytic disorders	Monocyte related monocytic leukemia H/DC sarcoma	**Malignant histiocytic disorders**

Table 2. LCH: Langerhans cell histiocytosis; JXG: Juvenile Xanthogranuloma; NLHC: non Langerhans cells histiocytosis; H/DC sarcoma: histiocytic/dendritic cell sarcoma.

The World Health Organization (WHO) has also made attempts to classify histiocytosis. The classification proposed by the WHO, divides them as macrophage or histiocyte related (Class 1): which includes mainly localized and generalized H/DC sarcoma; dendritic cell related (Class 2): which include localized or generalized LCH (2A), Langerhans cell sarcoma (2B), interdigitating dendritic cell sarcoma (2C) and follicular dendritic cell sarcoma (2D) [22]. However the classification proposed by the Histiocyte Society is used more frequently and will be utilized in this text.

1.3 Dendritic cell related histiocytosis

Dendritic cell related histiocytosis are mainly composed of LCH and JXG. While LCH has been studied intensively in the past [23], and has well recognized prognostic factors and clear treatment guidelines [24], prognostic factors and treatment of NLCH, particularly of JXG remain less clear [25,26]. With this in mind we will discuss LCH superficially and discuss and review JXG with more detail.

1.3.1 Langerhans cell histiocytosis

The most frequent form of histiocytosis is LCH. It is a very heterogenous disorder with a broad clinical spectrum. It goes from an acute, fulminant, disseminated disease called Letterer-Siwe disease, to indolent and chronic lesions of bone or other organs called eosinophilic granulomas. The intermediate clinical form is called Hand-Schüller-Christian disease which is characterized by multifocal, chronic involvement and classically presents as the triad of diabetes insipidus, proptosis, and lytic bone lesions [27]. A congenital, self-healing form called Hashimoto-Pritzker disease has also been described [28].

1.3.1.1 Etiology and associated conditions

The etiology of LCH remains unknown. Several human herpesvirus have been suggested to play a role in the pathogenesis, but currently there is no evidence to support this theory [29]. In 1994 Willman et al. [30] first described that LCH as a clonal disease. By means of X-chromosome inactivation analysis they found, that disseminated and focal forms of LCH are clonal neoplastic disorders, that arise from somatic mutations leading to the expansion of Langerhans cells. Prior to this discovery the prevailing opinion was that LCH was a reactive disorder rather than a neoplastic disease. Analyzing the data recollected by the Histiocyte Society, Egeler et al. [31] reported two patterns of associations between LCH and other disorders. They found that retinoblastoma and ALL frequently preceded cases of

LCH and the chemotherapy used for LCH may have promoted secondary malignancies [31,32].

1.3.1.2 Histopathological features:

LCH lesions typically appear granulomatous, with a reactive background of macrophages, eosinophils and multinucleated giant cells. Malignant Langerhans cells which resemble normal Langerhans cells of the skin are pathognomonic [20,23]. They consists of large, ovoid, mononuclear cells, with a folded nucleus, a discrete nucleolus, and a moderate amount of slightly eosinophilic homogeneous cytoplasm. The Birbeck granule is their distinctive ultrastructural hallmark, which consists of an membranous body that possesses a short, rodlike shape. Langerhans cells also contain laminated substructures of lysosomes, tuboreticular structures, and trilaminar membranous loops [23]. The classical immunohistochemical markers of LCH are CD1a, S-100 and Fascin [33].

1.3.1.3 Treatment

The Histiocyte Society has conducted a number of prospective, randomized control trials to study various chemotherapeutic regimens in the treatment of LCH [15,34]. The choice of therapy is based on disease severity. The International LCH Study protocol of the Histiocyte Society proposes the stratification of LCH cases by the number of systems involved [15]. They further categorize those cases with single-system involvement by the number of sites within that system. In addition, the presence or the absence of risk-organ dysfunction is used to stratify patients with multisystemic disease; the presence of risk-organ dysfunction means a poorer prognosis. The patients are treated according to their stratification.

1.3.2 Juvenile Xanthogranuloma

The most frequent form of NLCH is Juvenile Xanthogranuloma. It is usually a benign, self limited histiocytic disorder of the skin, that appears mostly during the first year of life [35]. It was first described by Adamson in 1905 who named it congenital xanthoma multiplex . Helwig and Hackney demonstrated that these lesions had no relation to naevi or endothelial cells and proposed the term juvenile xanthogranuloma on the basis of the histologic findings of lipid laden histiocytes and giant cells [36]. The first extracutaneous site was reported by Lamb and Lain in 1937. They reported a patient with involvement of the lung, however no biopsies were performed of these lesions [37]. Since then, there have been several reports of biopsy-proven JXGs at extracutaneous sites, including systemic forms of this disease [35,38,39].

1.3.2.1 Epidemiology

The real incidence of JXG is unknown, but it may be higher than appreciated, since JXG occurs early in life, often as solitary lesions, that regress within several years, and are often mistaken for innocent “moles” [35,40]. A male predominance has been noted in childhood, estimated at 1.5:1 [41]. Most tumors appear early in life, approximately 5-17% are present at birth and 40-70% appear during the first years of life [40,42]. Onset during adulthood has also been reported with a peak incidence in the late twenties to early thirties [43-46].

1.3.2.2 Clinical Findings

JXG is usually a well-demarcated, firm, rubbery round to oval papule or nodule usually varying form 0,5 to 2 cm in diameter. In early stages it is pink to red with a yellow tint, but with time it acquires a yellow-brown hue and may develop occasional telangiectasias on the surface [35]. **(See Figure 2)** However, the shape, location, distribution and size can

vary greatly resulting in unusual clinical forms of JXG. Although most cases have a self limited course, in 4-5% extracutaneous tissues are involved [42]. Systemic JXG is defined as an involvement of two or more visceral organs in addition of multiple cutaneous and subcutaneous lesions [43]. Although systemic JXG typically has a benign clinical course and does not require therapy, it can lead to significant morbidity or even be fatal particularly when the central nervous system or the liver are involved [38,43,47].

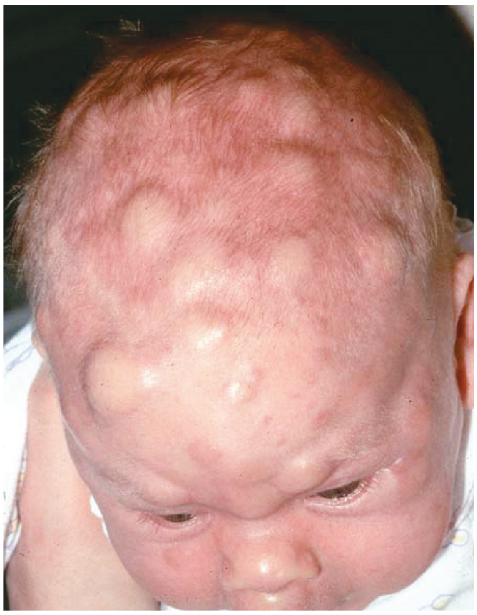

Figure 2. Shows characteristic well-demarcated, firm, rubbery round to oval dermal lesions in an infant. Taken from **[48]**.

1.3.2.3 Associated Conditions

The association between JXG and pigmentary abnormalities, particularly in patients with café-au-lait spots, was first suggested by Marten and Sarkany [49]. Since then, several patients with JXG, café-au-lait spots, and a family history of neurofibromatosis type 1 have been reported [35,41,50,51]. Other well documented association is that of juvenile chronic myelogenous leukemia (JCML). In most cases, the JXG antedates or is noted at the same time the leukemia is diagnosed [41,52,53]. In children with JCML the JXG lesions are usually multiple [53], but solitary lesion have been reported [35]. The relation of JXG with

this type of leukemia is of particular interest since there is a known association of between JCML and neurofibromatosis type 1 [54]. By performing a systematic review of the literature Zvulunov et al. estimated that children with NF and JXG have a 20 to 32-fold higher risk for JCML than do patients with NF who do not have JXG [41]. They conclude that a finding of JXG in an infant with neurofibromatosis should alert a physician to a possible development of JCML [41]. There are single reports of hematologic conditions that appeared in association with classical JXG. In children these include pre-B ALL, monocytic leukemia and myelomonocytic leukemia [35,38,55,56]. In adults they encompass B-cell acute lymphoblastic leukemia, large B-cell lymphoma, chronic lymphocytic leukemia, monoclonal gammopathy, essential thrombocytosis and adult T-cell leukemia/lymphoma [44,46]. Also single associations with urticaria pigmentosa, Niemann-Pick disease and possibly cytomegalovirus infection have been reported [57-59].

1.3.2.4 Histopathologic features

JXG are characterised by a dense, sheet-like, non-encapsulated, well-demarcated, histiocytic infiltrate and the presence of foamy or Touton giant cells, within the papillary dermis or the papillary and reticular dermis. Extension into subcutaneous tissue, fascia, and peripheral muscle occurs in up to 38% of cases [45,60,61]. In addition to histiocytic cells, many cases show a variable admixture of lymphocytes and eosinophilic leukocytes [62]. In early stages many histiocytes with a small degree of lipidization are intermingled with a scanty inflammatory infiltrate. In older lesions, the histiocytes have a vacuolated, foamy, xanthomatous cytoplasm and there are more inflammatory cells, giant cells and Touton cells [35,62]. **(See Figure 3)**

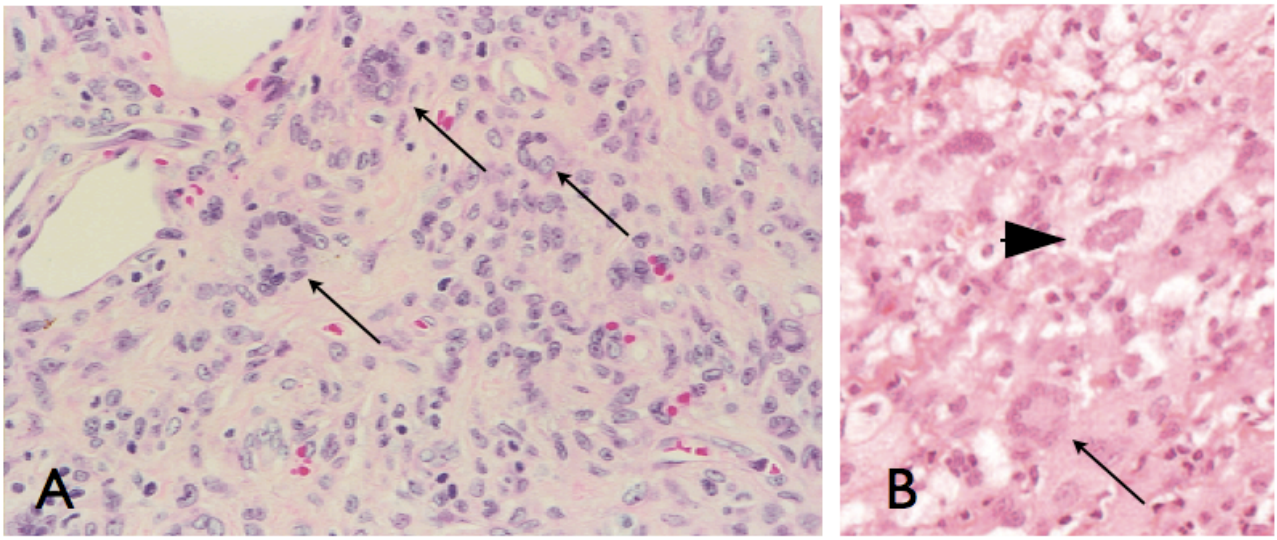

Figure 3. A) Skin biopsy taken from a patient with JXG and stained with hematoxylin-and-eosin (H&E). It shows the classic mixture of mononuclear cells, lymphocytes, xanthoma cells, and scattered Touton giant cells (arrows). Modified from [63]. B) Skin biopsy from a different patient, stained with H&E showing histiocytes with a vacuolated foamy, xanthomatous cytoplasm, (arrowhead) and a Touton giant cell (arrow). Modified from [64].

Ultrastructurally, the histiocytes of early lesions have an irregular nucleus and are rich in pseuopods lysosomal structures and dense bodies; Birbeck granules are usually absent [26,65,66]. Immunohistochemical staining of JXG lesions show expression of factor XIIIa, CD68, CD164, fascin, HLA-DR, and CD14. They are negative for S100 and CD1a [26,62,67]. These characteristics and the absence of Birbeck granules are the main histological differences between LCH and JXG.

1.3.2.5 Pathogenesis

Currently, no conceptual framework regarding the etiology and pathogenesis of JXG exists. The first hypothesis of the cellular origin of JXG was made in 1912 by McDonagh, who suggested an endothelial cell as the source of the lesion [68]. In 1954, Helwig and

Hackney emphasized the fibrohistiocytic nature of this entity [36]. Since then, JXG has been designated as a benign proliferative macrophage disorder [1], a histiocytosis of factor XIIIa+ dermal dendrocytes [69], a lesion related to indeterminate cells [47], or as a dendritic cell-related histiocytic disorder [20]. Kraus et al considered the CD4+ plasmocytoid monocyte to be the principal element of JXG, based on the occurrence of extracutaneous forms, and the CD4 reactivity found on some JXG lesions [63]. However, despite the controversies regarding its cellular origin, the term JXG is widely accepted [62]. Recently Janssen et al. described that, similar to LCH, JXG is a clonal proliferation of histiocytic/dendritic cells, proving that JXG is a neoplastic disease [70].

1.3.2.6 Differential diagnosis

The differential diagnosis of JXG includes several disorders with similar clinical or histologic features. The nodular lesions of LCH can display similar clinical features but can ruled out by histologic, immunohistochemical and ultrastructural findings. In self healing reticulo-histiocytosis (Hashimoto-Pritzker disease), which is considered part of the spectrum of LCH, the lesions often ulcerate and regress rapidly in approximately 2 to 3 months. Other differential diagnosis that should be considered are: benign cephalic histiocytosis, papular xanthoma, xanthoma disseminatum, tuberous xanthoma, solitary mastocytoma and Sptiz nevus [35,48].

Sometimes atypical clinical forms of JXG can mimic dermatofibromas, dermal nevus, calcinosis cutis, pyogenic granuloma, xanthoma or keratoacanthoma. JXG located in deep tissues may be mistaken for malignant tumors such as rhabdomyosarcoma, fibrosarcoma, or malignant fibrohistiocytoma. However most patients with visceral involvement also have cutaneous lesions, which can aid the diagnosis [35,71]. **Table 4** shows lesions with clinical and histological resemblance to JXG.

Table 4. Differential diagnosis of JXG divided in clinical and histological resemblance [35,48,63].

Differential diagnosis of JXG	
Histiocytosis	**Clinical Resemblance** LCH Hashimoto-Pritzker Disease Benign cephalic histiocytosis Papular xanthoma Xanthoma disseminatum
Other neoplastic disease	**Clinical Resemblance** Solitary mastocytoma Spitz nevus **Histological resemblance** Keratoacanthoma Rhabdomyosarcoma Fibrosarcoma Malignant fibrohistiocytoma
Other pathologies	**Clinical Resemblance** Tuberous xanthoma **Histological resemblance** Calcinosis cutis Pyogenic granuloma Dermatofibroma Xanthoma Dermal nevus

1.3.2.7 Treatment

For most localized forms of JXG no specific treatment is required, since the lesions often resolve spontaneously. In visceral and disseminated lesions a systemic treatment is usually necessary, since they often have an aggressive course and do not resolve spontaneously [26]. However there is still no consensus on which chemotherapeutic agents should be used [26]. Stover et al., recommend treating systemic JXG based on LCH protocols, due to the lack of standardized treatment and the great similarity between disseminated forms of LCH and JXG. **Table 5** shows a literature review of treatment regimens used so far to treat systemic JXG.

Table 5. Synopsis of the treatment of systemic JXG, including current case. Adapted from [26].

Reference	Sites of disease	Age at Dx	Sex	Treatment	Outcome/ Observation period
Stover [26]	Skin, lung, kidney, bone, CNS	10 m	F	VBL, VP16, MTX, LV, 6-MP, PDN 6-MP, MTX	NED/27 m
Stover [26]	Skin, pituitary, bone marrow	16 y	M	PDN VBL, MTX, LV, PDN	AWD/10 m
Dölken [121]	Liver, lung, kidney, bone, CNS, intestine	7 m	F	PDN, VBL, VP16+ IT MTX, PDN 6-MP +IT MTX, PDN	AWD/5 y
Janssen [62]	Skin, liver, spleen	1 m	M	VBL, PDN, IG	NA
Janssen [62]	Skin, liver, lung, kidney, CNS, bone marrow	7 m	M	PDN, VBL, MTX, 6-MP Partial excision CNS	AWD/21 m
Janssen [62]	Skin, liver, lung, kidney, heart, spleen, intestine, bone marrow	0 d	F	VP16, DEX, IVIG	DOD/ 34 d
Chantranuwat [120]	Liver, bone, marrow	2 m	F	VBL, VP 16	NED/2 y
Nakatani [119]	Skin, liver, skin, CNS, soft tissue	0 d	F	ARA-C, VCR, PDL MTX, PDL	AWD/24 m
Dehner [43]	Liver, lungs, kidney, bone	18 m	M	VBL, PDN	AWD/1 y
Dehner [43]	Lungs, kidneys, bone, CNS	5 m	M	PDN, VBL, MTX 2-CDA	AWD/4 m
Labalette [118]	Skin, liver, lung, kidney, spleen, CNS, testis, retina	8 m	M	VBL PDN	AWD/24 m
Freyer [38]	Skin, lung, CNS	6 m	M	VBL, PDN VP16, MPDL 6-MP, MTX	NED/8 y
Freyer [38]	Skin, liver, soft tissue	1 w	M	CSA CSA MPDL, VBL	NED/8 y
Eggli [117]	Skin, kidney, bone	3 m	F	VBL	AWD/3 y
Eggli[117]	Liver, bone, adrenal	3 d	F	MPDL VP16	NED/21 m
Flach [116]	Skin, CNS, soft tissue, eye	12 y	M	Clofibrate, VBL CPM, 5FU, MTX	DOD/8 y
Unuvar [115]	Skin, liver, lung, kidney	10 y	M	MPDL	AWD/1 y

Reference	Sites of disease	Age at Dx	Sex	Treatment	Outcome/ Observation period
Perez-Becker [72]	Skin, lung, kidney, gastrointestinal tract.	5 y	F	VCN, adriamycin, MTX, asparaginase,cyclophosphamide, MTX, VBN, PDN, VP-16	DOD/252 d

Table 5. Synopsis of the treatment of systemic JXG, including current case. Dx: diagnosis, VBL: Vinblastine; PDN: prednisone; PDL: prednisolone; IVIG: intravenous immunoglobulin; VP16: etoposide; DX: dexamethasone; LV: leucovorin; 5FU: 5-fluorouracil; MPDL: methylprednisolone; 2-CDA: 2-chlorodeoxyadenosine; CsA: cyclosporine; VCR : vincristine; ARA-C: cytarabine; CMP: cyclophosphamide; IT: intrathecal; CR: complete response; NED: no evidence of disease; AWD: alive with disease; DOD: dead of disease; NA: not available

As can be appreciated the exact pathophisiology of JXG is still unknown, this contributes to a lack of clear treatment guidelines in patients who present systemic forms of this disease. The co-occurrence of T-ALL and JXG in a patient treated at our hospital gave us the unique opportunity to study more closely this rare disease form.

2. OBJECTIVES

2.1 General Objective:

The objective of this thesis is to test the hypothesis that a relationship exists between a pathological differentiation within the lymphoid lineage and the pathogenesis of histiocytosis, particularly between T-ALL and a systemic form of NLCH (JXG). The co-occurrence of these two malignancies in a single patient gave us the opportunity to analyze if there was a clonal relationship between them.

2.2 Specific Objectives:

1. Present evidence from a particular case in which T-ALL and a systemic form of NLHC (JXG) coincided in a single patient [72].
2. Perform a systematic literature review to search for a possible relationship between pathological differentiation within the lymphoid lineage and the pathogenesis of histiocytosis.

3. MATERIAL AND METHODS

3.1 Literature review

We performed a systematic search in Pubmed with following search criteria:

- clonal relationship
- histiocytosis
- Langerhans cell histiocytosis
- non Langerhans cell histiocytosis
- malignant histiocytic disorder
- leukemia
- lymphoma
- lymphoid origin
- IgH, TCR rearrangment
- hematologic malignancy
- histiocytic sarcoma
- juvenile xanthogranuloma
- Rosai Dorfman

We also analyzed the references within each article to find further cases. Only case reports and case series where a clear genetic or molecular association existed between the primary hematologic malignancy and the secondary histiocytosis were included. We did not include case reports and case series which did not show a genetic or molecular association between malignancies. Deadline for the literature search was February 2011. Cases with monocytic leukemia were excluded due to their known presentation as biphenotypic leukemias with histiocytic markers [73]. Also cases of JCML were excluded due to the known relationship between JXG and this type of myelogenous leukemia.

A total of 21 articles were found, 3 of which analyzed the clonality amongst cells of patients which had only LCH [30,74] or JXG [70] without other malignancies. Two analyzed the lymphoid genetic markers in LCH [8] and histiocytic sarcomas [7] respectively and 2 case reports [75,76] lacked a molecular analysis of one of the two malignancies leaving a total of 14 articles, which included a total of 29 patients.

3.2 Case report

This case was published in Pediatric Blood and Cancer 2010 [72].

A five-year-old female presented with lymphadenopathy, hepatosplenomegaly and disseminated petechiae. Initial laboratory examinations revealed anemia (Hb 10.5 g/dl), thrombocytopenia (60,000/μl), and marked leukocytosis (366,800/μl). A chest X-ray showed an enlarged mediastinum consistent with a mediastinal mass. Flow cytometry of peripheral blood revealed a population of blasts expressing CD1a, CD2, CD4, CD7, CD8, CD45 and cyCD3; negative for CD13, CD14, CD15, CD33, CD41, Glyc A and cyMPO. Cytogenetic analysis revealed a normal karyotype that was negative for BCR-ABL, MLL-AF4 and TEL-AML1.

The patient was treated according to the cooperative study group for childhood acute lymphoblastic leukemia (COALL) 07-03 High-Risk protocol consisting of vincristine, daunorubicin, methotrexate, prednisone, cyclophosphamide, asparaginase, cytarabine and etoposide. After completion of the induction phase, on day + 28 of the protocol, the enlarged lymph nodes and the hepatomegaly had regressed. At this point, the chest x-ray also showed regression of the mediastinal mass, cerebrospinal fluid and bone marrow were free of blasts, indicating a complete remission of the T-ALL. She tolerated the intensive-phase of the chemotherapeutic protocol without major complications. Throughout the therapy block with methotrexate she presented recurrent grade 2 mucositis which

responded well to symptomatic treatment. She presented once fever, which was treated with antibiotic therapy and required twice a packed red blood cell and once a platelet transfusion. No other complications were documented. During the central nervous system (CNS)-phase of the protocol, on day + 153 after starting the treatment, a firm non-tender left cervical mass was noted **(Figure 4).**

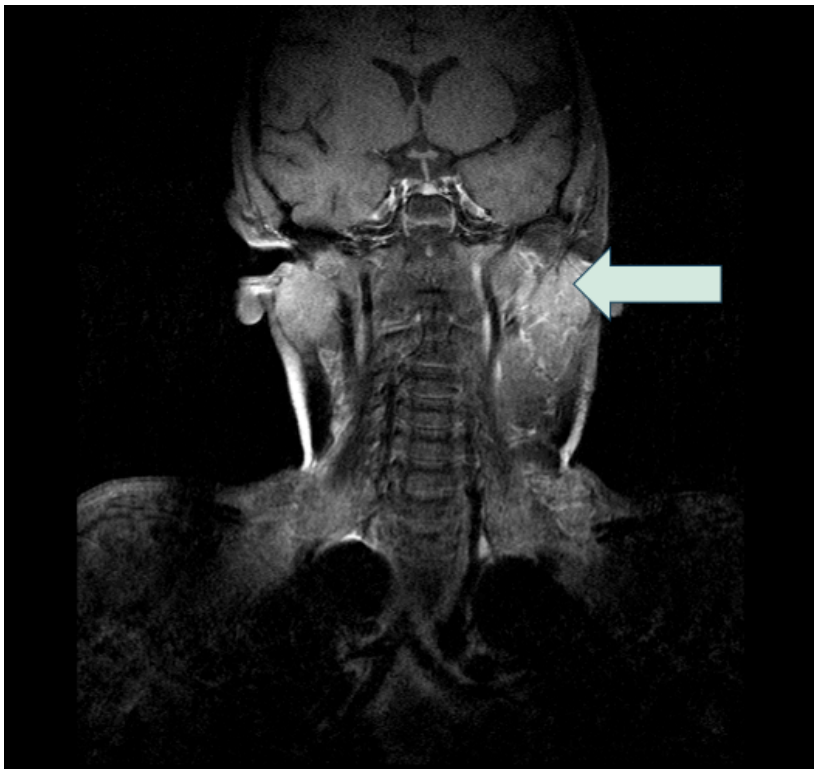

Figure 4. Magnetic resonance imaging (MRI) scan of the cervical region at day +188 of the COALL treatment protocol showing a large cervical mass. (Institute of Radiology, Professor Dr. med. Fiedler, Helios Klinikum Krefeld)

To exclude a nodal relapse of the T-ALL, a partial excision of the cervical tumor was performed on day +172, 19 days after the last cranial radiation, and both systemic and intrathecal chemotherapy. Histologically the cervical lesion corresponded to a histiocytic

tumor composed of large oval cells with ovoid nuclei and eosinophilic cytoplasm. Scattered multinucleated cells resembling Touton giant cells were noted **(Figure 5)**

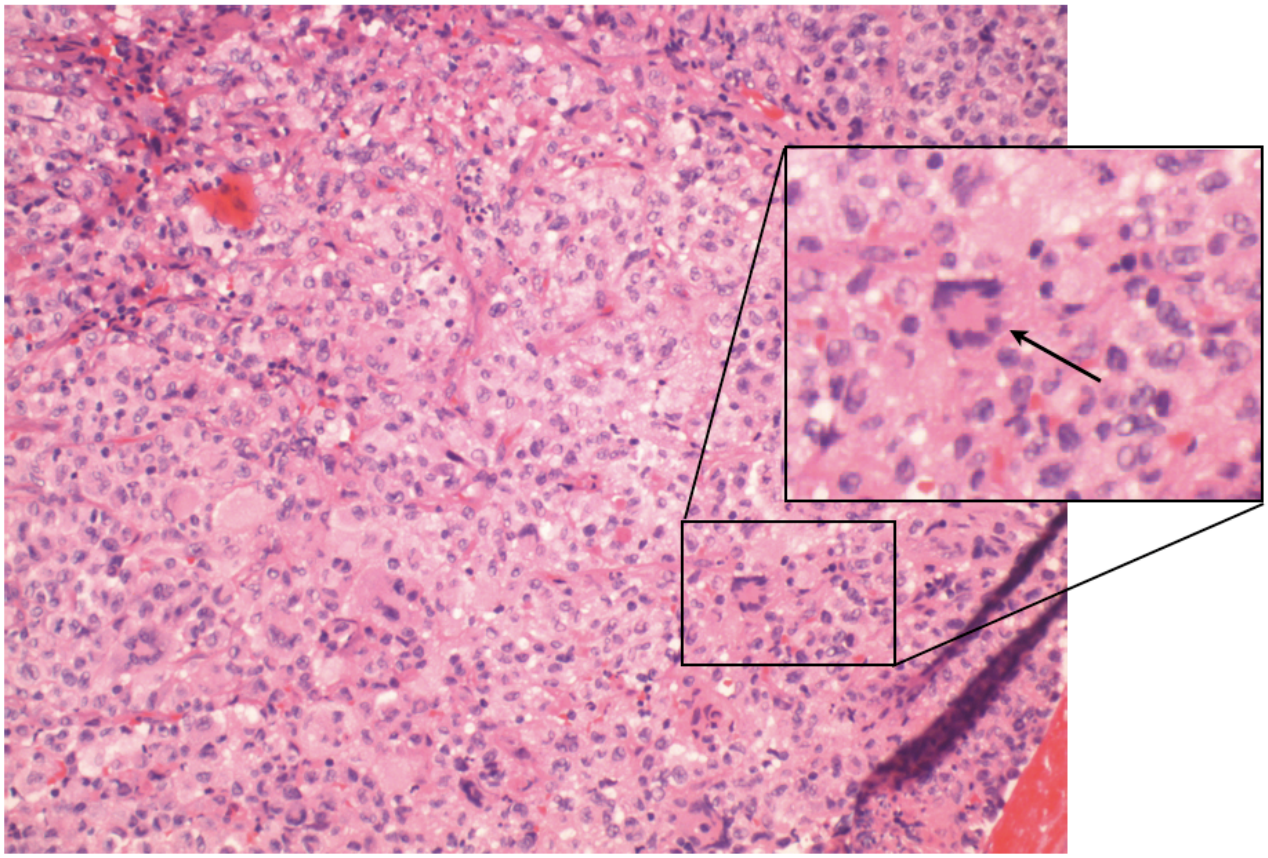

Figure 5. Histology of the partially resected tumor stained with hematoxylin and eosin 20 x reveals large oval cells with ovoid nuclei and eosinophilic cytoplasm, as well as Touton giant cells (arrows). (Institute of Pathology, Prof. Dr. med. Michael Gokel, Helios Klinikum Krefeld)

Immunohistochemical analysis demonstrated expression of CD68, Factor XIIIa, CD4 and Fascin in the tumor cells. Negative immunohistochemical reaction was found for CD1a, langerin, CD30, pan-cytokeratin, ALK1, CD2, CD8 and CD 56 as well as CD3 **(Figure 6 A).** These findings led to the diagnosis of JXG. Interestingly the tumor displayed high proliferation markers with abundant mitotic figures and a high Ki67-index of 50% **(Figure 6 B)**, which are unusual for JXG [77].

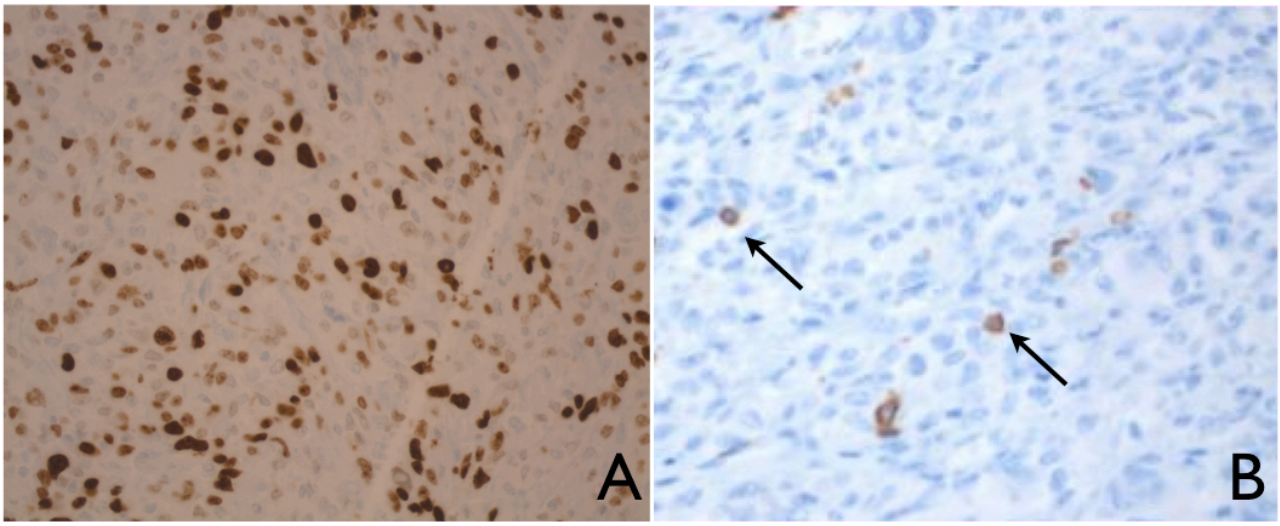

Figure 6. A) Immunohistochemistry for Ki-67 depicts a proliferation index of approximately 50%. **B)** Immunohistochemistry for CD3 marks single T cells, probably tumor infiltrating reactive T-lymphocytes (arrows). (Institute of Pathology, Prof. Dr. Ivo Leuschner; PD Dr. Wolfram Klapper, University Hospital Schleswig-Holstein, Hematopathology Section and Lymph Node Registry Kiel)

One month after the partial removal the cervical tumor had regained its original size. A re-induction course according to the COALL 07-03 High-Risk protocol was administered consisting of vincristine, adriamycin, asparaginase, methotrexate and cyclophosphamide. However, the tumor continued growing, extending to the submandibular and occipital regions. Due to the rapid growth of the JXG and the increasing risk of airway obstruction, a second surgical resection was performed on day + 214. At this point, the tumor had infiltrated cervical and upper thoracic tissues, extending from the left arm plexus to the base of the skull, making a complete resection impossible. Histologic analysis of the tissue obtained during this procedure was consistent with the histological and immunohistochemical findings of the first biopsy. After the second surgery, the tumor continued growing and soon a subsequent computed tomography demonstrated its dissemination to the lungs, thus on day +228 it was decided to administer chemotherapy consisting of methotrexate, vinblastine, prednisolone and etoposide according to the Arm

B of the Langerhans cell histiocytosis (LCH) III protocol of the Histiocyte Society. Although this protocol induced a modest reduction of the pulmonary lesions, the patient's condition deteriorated. Despite intensive care the patient died of cardiopulmonary arrest on day + 252 after the initiating treatment for the T-ALL, 80 days after the histological diagnosis of an aggressive JXG. The autopsy revealed a massive infiltration of the liver, kidneys, lungs and gastrointestinal tract by the JXG **(Figure 7).**

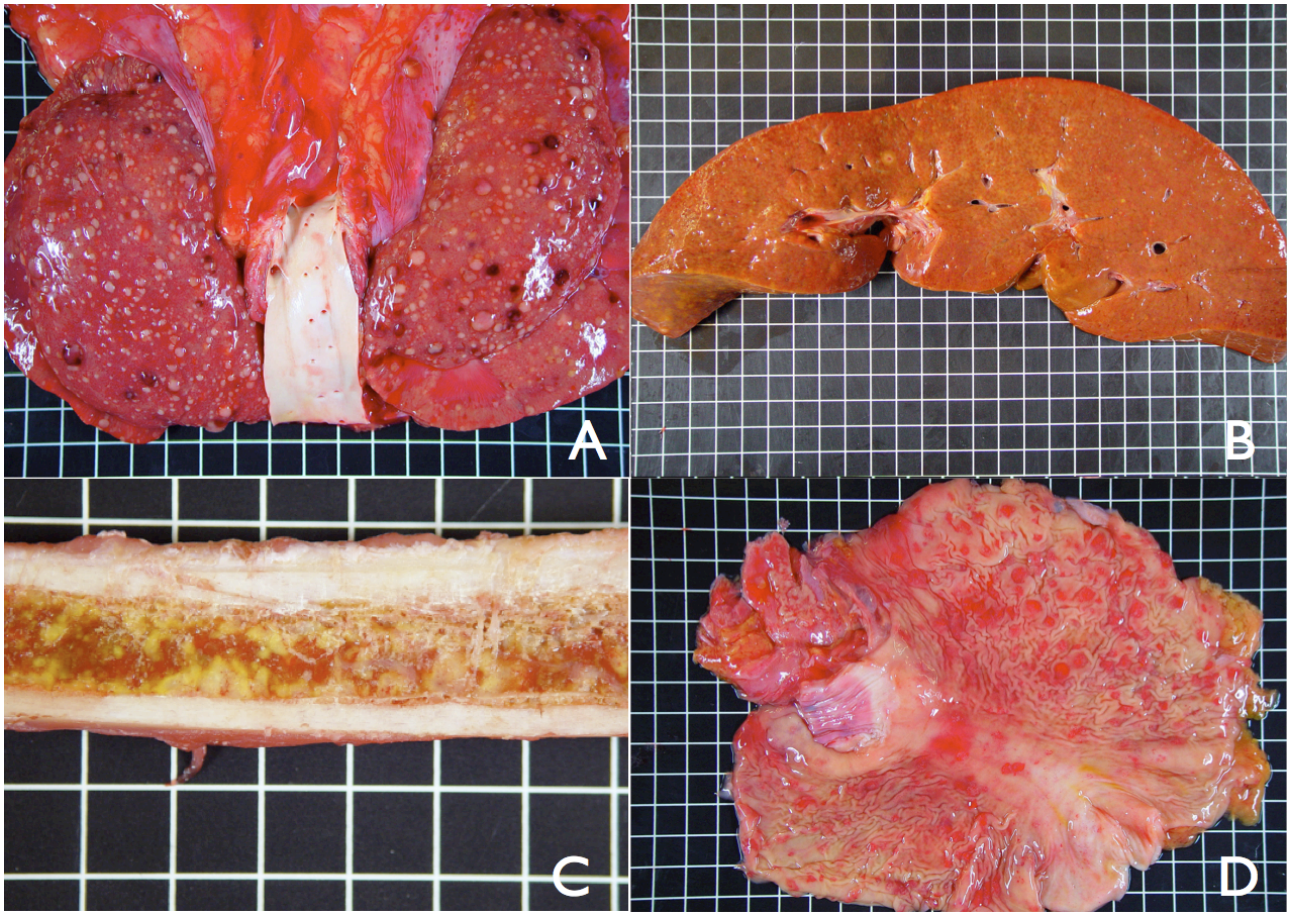

Figure 7. Autopsy findings: **A)** Kidneys show a macroscopically visible dissemination of the JXG infiltrates. **B)** The infiltrate was also found in other organs such as liver, **C)** esophagus, **D)** stomach as well lungs, and spleen (not shown). (Institute of Pathology, Prof. Dr. med. Michael Gokel, Helios Klinikum Krefeld)

T-cell receptor rearrangement analysis

(Performed by Dr. rer. nat. Monika Szczepanowski, Institute of Pathology, University Hospital Schleswig-Holstein, Kiel)

The human antigen-specific TCR molecule is a heterodimer composed of disulfide-linked α- and β-polypeptide subunits. Each of these genes undergoes site-specific recombination that generates, at the DNA level, the sequence diversity that allows a wide repertoire of antigen specificity, in a manner analogous to the immunoglobulin genes. **(See Figure 8)** The rearrangement of the TCR-α/β and γ genes is unique to every T-cell clone and hence, sequence analysis can be used to establish clonality and lineage derivation within leukemias of T-cell progenitors [78,79].

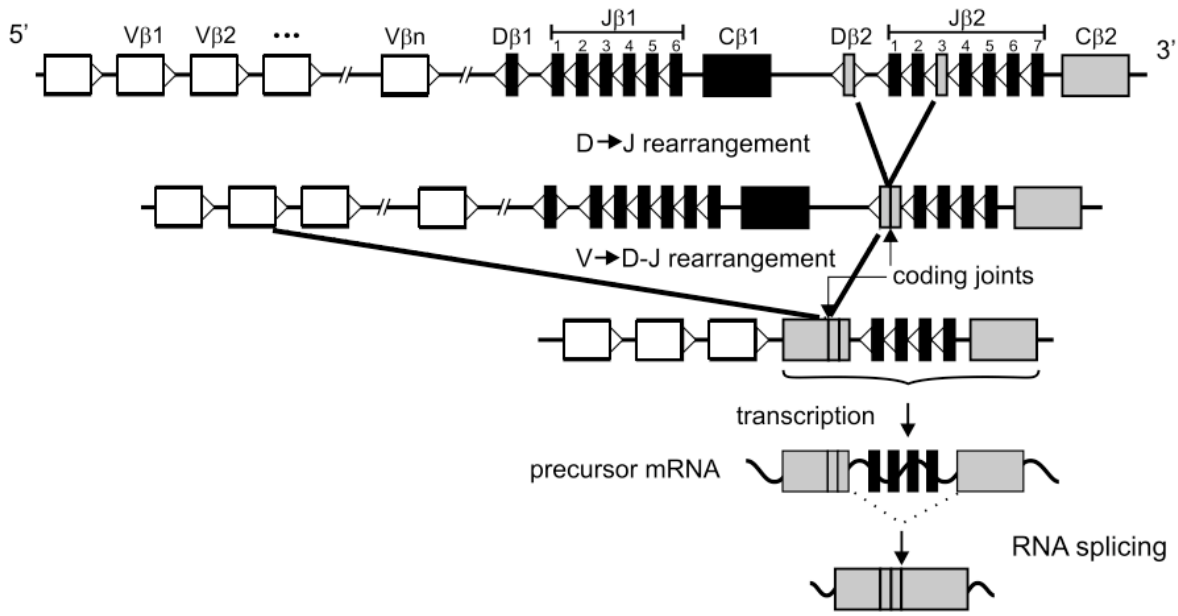

Figure 8. Schematic diagram of sequential rearrangement steps, transcription, and translation of the TCR-β gene. Based on **[80]**.

TCR-γ gene rearrangement represent the “prototype” of restricted repertoire targets [80]. It is preferred for clonality analysis since it is rearranged early in T-cell development, probably just after TCR-δ in both TCR-α/β and TCR-γ/δ lineage precursors [81]. Unlike several other Ig/TCR loci, the complete genomic structure of TCR-γ has been known for many years, and it contains only a limited number of Vγ and Jγ segments. Thus the amplification of all major Vγ–Jγ combinations is possible with four Vγ and three Jγ primers making it ideal for clonality analysis [80]. **(See Figure 9)** It is rearranged in more than 90% of T-ALL, T-cell large granular lymphocyte leukemia, and T-cell polymorphic leukemias, as well as in approximately 50–75% of peripheral T-non-Hodgkin lymphomas and mycosis fungoides but not in true NK cell proliferations. It is also rearranged in a major part of B-lineage acute lymphoblastic leukemias, but much less so in B-non-Hodgkin lymphoma [80,82-84].

Figure 9. Schematic diagram of the human TCR-γ locus on chromosome band 7p14. Only the rearrangeable Vγ gene segments are depicted in white (functional Vγ) or in gray (nonfunctional Vγ). Taken and adapted from [80].

Samples

(Performed by Dr. rer. nat. Monika Szczepanowski, Institute of Pathology, University Hospital Schleswig-Holstein, Kiel)

As published in [72]. T-ALL blast DNA was obtained from the patients’ peripheral blood drawn at day -7 of treatment start. DNA from JXG biopsies obtained on day +172 and

+214 (+172 JXG and +214 JXG) was isolated from full slides of formalin-fixed and paraffin-embedded infiltrated lymph nodes with QIAamp Mini DNA Kit (Qiagen, Hilden, Germany). JXG-cells were microdissected from +214 JXG samples. In order to exclude T-cells, the slides were previously stained for CD3. (MMI Cell-Cut System, MMI AG, Glattbrugg, Switzerland). DNA from micro-dissected JXG-cells (MDJXG) was extracted using the ChargeSwitch Forensic DNA Purification Kit (Invitrogen, Karlsruhe, Germany).

Analysis

(Performed by Dr. rer. nat. Monika Szczepanowski, Institute of Pathology, University Hospital Schleswig-Holstein, Kiel)

The clonality analysis was performed at the Pathology Institute at the University Clinic Kiel as published in [72]. TCR-γ rearrangements were analyzed using BIOMED-2-primers va mix, vb mix, JG1.1/1.3 mix, VGlf (degenerate primer component of the va mix) and JG1.3 [80]. **(See Table 5)** PCR products were cloned into pCR2.1 TOPO vector and expanded in TOP10F´ E. coli (TOPO TA Cloning Kit, Invitrogen, Karlsruhe, Germany). Plasmids were isolated using the QuickLyse Miniprep Kit (Qiagen, Hilden, Germany), sequenced (BigDye v1.3, Applied Biosystems, Darmstadt, Germany), purified (NucleoSEQ Columns, M&N GmbH & Co., Düren, Germany) and analyzed using the ABI PRISM 310 Genetic Analyzer capillary electrophoresis (Applied Biosystems, Darmstadt, Germany). Sequence alignments were performed using the NCBI Blast database [85]**.**

Table 5. Sequence of the BIOMED 2 primers used to perform PCR.

TCRG va mix			
Vγlf (-178)	5'-GGAAGGCCCCACAGCRTCTT-3'	**Jγ1.1/2.1** (+64)	5'-CGAGTATCATTGAAGCGGACCATT-3'
Vγ10 (-126)	5'-AGCATGGGTAAGACAAGCAA-3'	**Jγ1.3/2.3** (+38)	5'-GAGAAACCGTCACCTTGTTGTG-3'
TCRG vb mix			
Vγ9 (-141)	5'-CGGCACTGTCAGAAAGGAATC-3'	**Jγ1.1/2.1** (+64)	5'-CGAGTATCATTGAAGCGGACCATT-3'
Vγ11 (-58)	5'-CRRCCACTTCCACTTTGAAA-3'	**Jγ1.3/2.3** (+38)	5'-GAGAAACCGTCACCTTGTTGTG-3'

Table 5. Sequence of the BIOMED 2 primers used to perform PCR. The relative position is of the Vγ and Jγ primers is indicated according to their most 50 nucleotide upstream (-) or downstream (+) of the involved recombination signal sequences. (Institute of Pathology, University Hospital Schleswig-Holstein, Kiel)

Figure 9 shows a schematic diagram of the regions amplified by each primer used. Only VGlf and JG1.3 efficiently amplified the rearranged alleles, whereas all other oligonucleotide combinations in va and vb mixes led to polyclonal background products or synthesized no product at all.

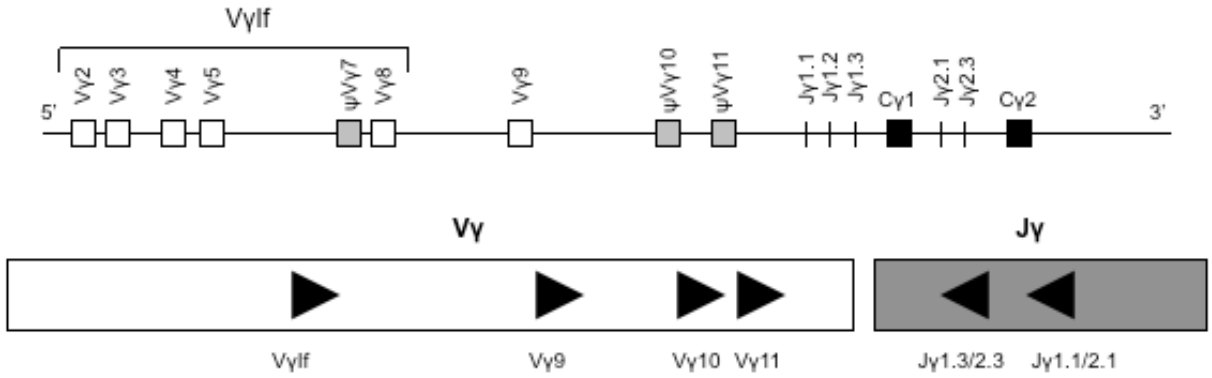

Figure 9. Schematic diagram of TCR-γ Vγ–Jγ rearrangement with four Vγ primers and two Jγ primers. Based on **[80]**.

4. RESULTS

4.1 Systematic Review

The articles found were case reports and case series of patients who presented hematologic malignancies and a histiocytosis that shared molecular characteristics. The results are summarized in **Table 6.** (Inclusion and exclusion criteria are presented in Material and Methods.) A total of 29 patients are reported, with an age range from 3 up to 67 years. A male predominance of 21(73%) vs 8 (27%) was found. All hematologic malignancies preceded the histiocytosis. Interestingly most secondary malignancies were either malignant histiocytosis 15 (51%) or atypical forms of histiocytosis 8 (27%) probably with an overall unfavorable prognosis. The interval between the malignancies ranged from a simultaneous appearance, to a time span of 14 years as reported by Dictor et al. [86]. They describe a patient who developed a H/DC sarcoma with a clonal BCR/ABL rearrangement 14 years after an acute lymphoblastic leukemia. They found a very similar IgH rearrangement in both malignancies suggesting that the junctional nucleotides continued evolving throughout time.

We divided the reported cases in two groups B-cell and T-cell related primary malignancies for further analysis. (21 cases of B-cell related primary malignancy vs 7 cases of T-cell related primary malignancy). The case reported by Dictor et al, doesn't specify the nature of the ALL , so it was not included in the group analysis [86]. B-cell related primary malignancies included: B-cell NHL, B-ALL and pre B-ALL. T-cell related malignancies included: T-ALL and T-lymphoblastic lymphoma.

Table 6. Literature review showing reports of proven clonal relationships between hematologic malignancies and histiocytosis.

Pt	Reference	Year	Age/ sex	1st neoplasm	2nd neoplasm	Interval 1-2 neoplasm (years)	Molecular analysis
1	Wu [87]	1999	F	B-NHL	Dendritic cell proliferation	Not known	HUMARA gene scan. (Only dendritic cell proliferations were analyzed)
2			F	B-NHL	Dendritic cell proliferation	Not known	HUMARA gene scan. (Only dendritic cell proliferations were analyzed)
3	Bouabdallah [99]	2001	19/M	B-ALL	True histiocytic lymphoma	4	Same IgH rearrangement in both tumors
4	Magni [88]	2001	Not known	B-NHL	LCH	Synch	Same IgH rearrangement in both tumors
5	Feldman [6]	2004	14/M	pre B-ALL	H/DC sarcoma	Synch	Same IgH and TCR-γ rearrangement in both tumors
6	Feldman [4]	2008	62/M	FL (B-NHL)	H/DC sarcoma	2	t(14;18) by FISH, BCL2/JH MBR, IgH, sequence similarity
7			30/F	FL (B-NHL)	H/DC sarcoma	12	t(14;18) by FISH, BCL2/JH MBR, IgH, sequence similarity
8			60/M	FL (B-NHL)	H/DC sarcoma	3	t(14;18) by FISH, BCL2/JH MBR, IgH
9			55/F	FL (B-NHL)	H/DC sarcoma	Synch	t(14;18) by FISH, IgH, sequence similarity
10			48/F	FL (B-NHL)	H/DC sarcoma	0,16	t(14;18) by FISH, BCL2/JH MBR, IgH, sequence similarity
11			62/M	FL (B-NHL)	H/DC sarcoma	Synch	BCL2/JH MBR, IgH
12			58/F	FL (B-NHL)	H/DC sarcoma	Synch	BCL2/JH MBR, IgH
13			67/M	FL (B-NHL)	H/DC sarcoma	0,58	BCL2/JH MBR, sequence similarity
14	Zhang [114]	2009	50/M	FL (B-NHL)	H/DC sarcoma	Synch	IGH/BCL2 rearrangement in both tumors
15	Castro [102]	2010	7/M	B-ALL	Atypical JXG	12	t(8;14) in both lesions
16			66/M	B-ALL	Atypical reticulohistiocytic lesion	0,5	Same IgH rearrangement in both tumors
17			66/M	B-ALL	Atypical histiocytic lesion	1,5	Trisomy 11 in both tumors
18			18/M	B-ALL	Atypical histiocytic lesion	1,3	Trisomy 5 in both tumors
19	McClure [113]	2010	25/M	B-ALL	H/DC sarcoma	0,33	Same IgH rearrangement in both tumors
20	Wang [104]	2010	61/F	B-NHL	H/DC sarcoma	1	IgH/BCL2 rearrangement in both tumors
21	Kumar [105]	2010	4/M	Pre B-ALL	H/DC sarcoma	Synch	Same IgH and TCR-γ rearrangement in both tumors and homozygous deletion of CDKN2A

Pt	Reference	Year	Age/ sex	1st neoplasm	2nd neoplasm	Interval 1-2 neoplasm (years)	Molecular analysis
22	Feldman [5]	2005	5/M	T-ALL	LCH	2	Identical TCR-γ rearrangements
23			8/M	T-lymphoblastic lymphoma	LCH	Synch	Identical TCR-γ rearrangements
24	Rodig [101]	2007	3/F	T-ALL	LCH	1,5	Identical TCR-γ rearrangements, and active NOTCH 1
25	Castro [102]	2010	5/M	T-ALL	H/DC sarcoma	0,5	p16 deletion on both chromosomes 9 in both lesions
26			8/M	T-ALL	LCH	2	Identical TCR-γ rearrangements
27			8/F	T-ALL	Atypical histiocytic lesion	1,41	Identical TCR-γ rearrangements
28	Perez-Becker [72]	2010	5/F	T-ALL	Atypical JXG	0,42	Identical TCR-γ rearrangements
29	Dictor [86]	2009	33/F	ALL	H/DC sarcoma	14	bcr/abl translocation found in H/DC sarcoma, and similar IgH rearrangements

Table 6. Literature review showing reports of proven clonal relationships between hematologic malignancies and histiocytosis. HUMARA: human androgen receptor, NHL: non-Hodgkin lymphoma; FL: follicular lymphoma; ALL: acute lymphoblastic leukemia; LCH: Langerhans cell histiocytosis; H/DC sarcoma: Histiocytic/Dendritic cell Sarcoma.

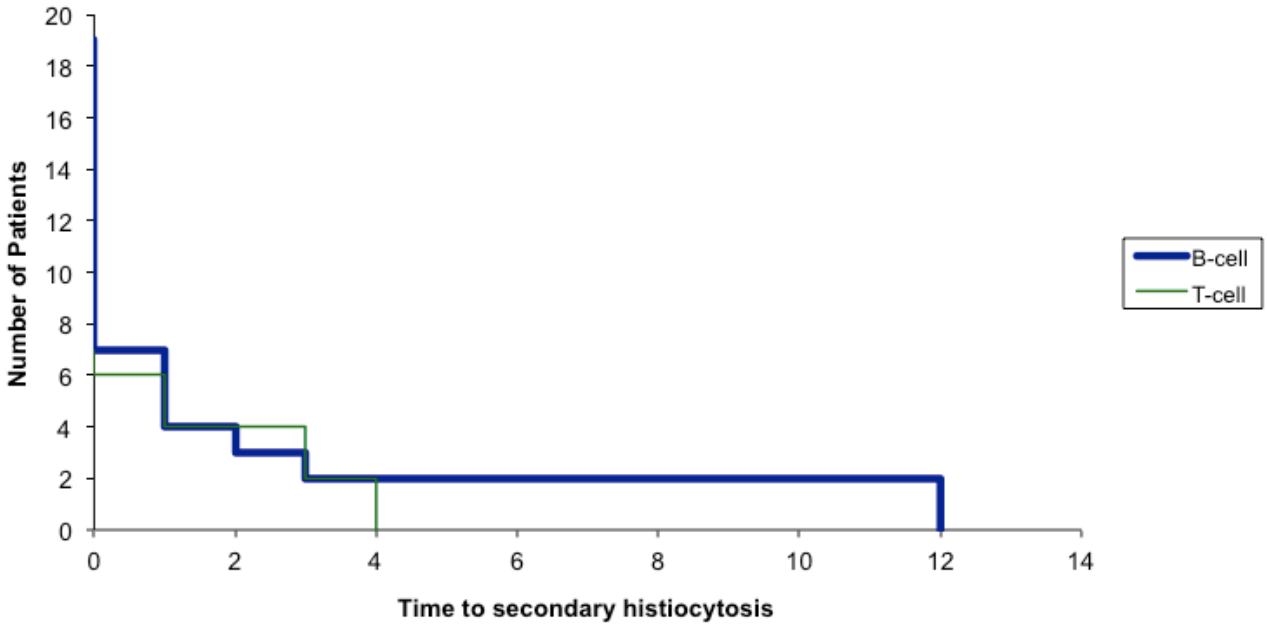

Figure 10. Time to B-cell and T-cell related secondary histiocytosis. Kaplan Meyer curve of the time to the secondary histiocytosis after the diagnosis of a B- and T-cell related primary malignancy. Of the total 21 Patients, with B-cell related malignancies, 2 were excluded because no information regarding the time to second disease was reported [87]. All 7 patients with T-cell related primary malignancies were included.

In B-cell related primary malignancies the interval between diseases ranged from a simultaneous appearance up to 12 years, as shown in **Figure 10**. The median was 0,5 years and the average was 2,23 years. In **Figure 10** one can observe that most secondary histiocytosis appear in the first 4 years of initial diagnosis, with a large proportion occurring simultaneously.

There were a total of 7 cases reported of T-cel related primary malignancies. The interval between diseases was from simultaneous to 4 years with a median of 1,41 years and an average of 1,11 years. (See **Figure 10)**

Figure 11 shows the distribution of secondary histiocytosis after B-cell and T-cell primary malignancies. Regarding B-cell primary malignancies the most frequent form of secondary histiocytosis corresponded to Histiocytic/Dendritic cell sarcoma with 61% (13/21). However one must consider that most these patient may be over-represented by the large case series of Feldman et al [4]. The second most frequent form of secondary histiocytosis were atypical histiocytosis with 19% (13/21). Interestingly LCH were only represented with 4% (1/21). Regarding T-cell related malignancies the most frequent form of secondary histiocytosis corresponded to LCH with 57% (4/7). The second most frequent form of secondary histiocytosis were atypical histiocytosis with 28% (2/7). Interestingly H/DCS were only represented with 14% (1/7).

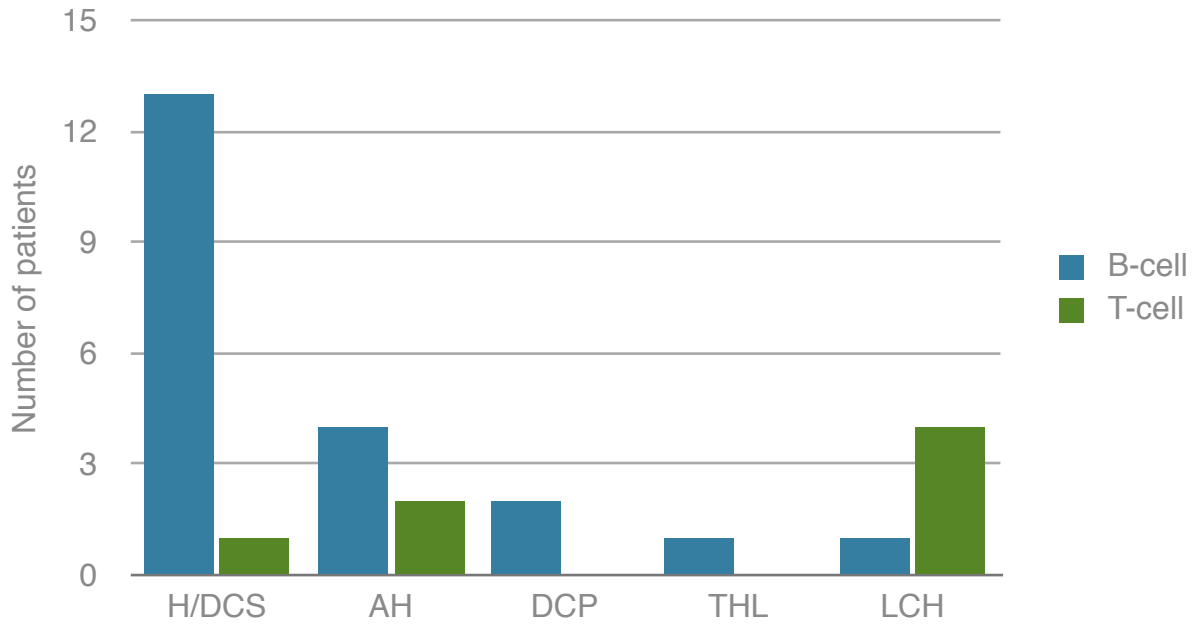

Figure 11. Distribution of B-cell and T-cell related secondary histiocytosis. H/DCS, Histiocytic/Dendritic cell sarcoma; AH, Atypical histiocytosis; DCP, Dendritic cell proliferation; THL, True histiocytic lymphoma; LCH, Langerhans cell histiocytosis.

There was a male predominance of almost 2:1 amongst B-cell related primary malignancies (13:7), in one case the sex of the patient was not reported [88]. We also found a male predominance in T-cell related primary malignancies with a male/female ratio of 4:3.

The age distribution amongst both B-cell and T-cell related primary malignancies differed greatly. B-cell related primary malignancies had an average age of onset of 42,8 years, and they appear to occur more frequently between the first two decades of life and after the sixth decade (**Figure 12).** In contrast T-cell related primary malignancies had an average age of onset of 6 years, and occurred between 3 and 8 years.

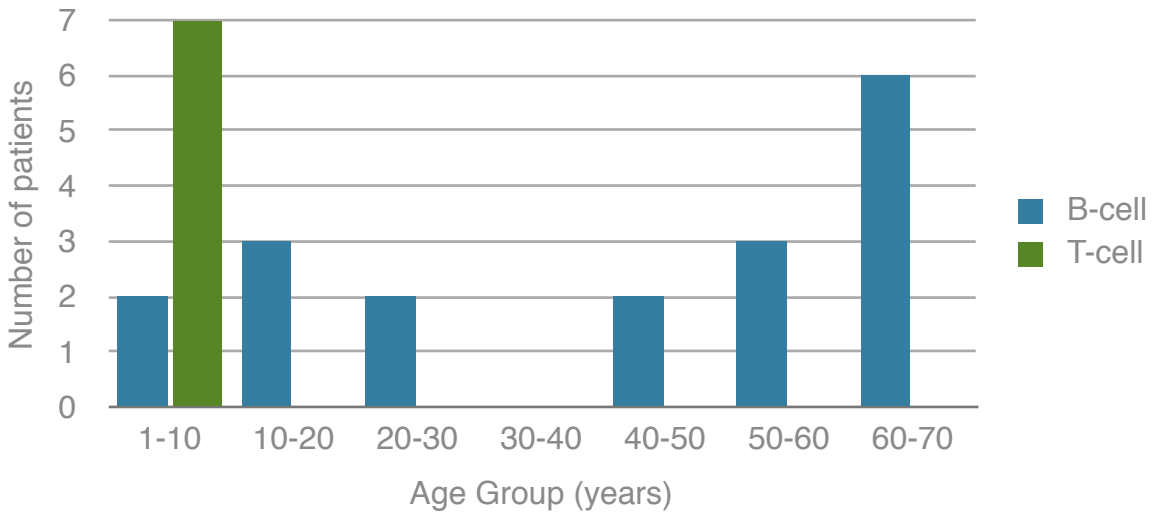

Figure 12. Age distribution of B- and T-cell related primary malignancies. (B-cell related malignancies in blue, T-cell related malignancies in green). Three patient with B-cell related malignancies were excluded since no data of age was provided [87,88].

4.2 Case report

Bi-allelic TCR-γ rearrangement in T-ALL and JXG (Institute of Pathology, University Hospital Schleswig-Holstein, Kiel)

Since there was no cytogenetic abnormality detectable in the T-ALL that might have served as a clonal marker of the disease, we evaluated TCR-γ rearrangements in the T-ALL and the JXG. At first, fragment analysis was performed using DNA obtained from T-ALL blasts from patient's peripheral blood taken at the time of diagnosis (on day -7 of treatment start), as well as from full sections of +172 JXG and +214 JXG. Fragment analysis performed with the BIOMED-2 degenerated oligonucleotide mix va/JG1.1-JG1.3, designed for multiplex or rearrangement-specific amplification of TCR-γ V-segments 2, 3, 4, 5, 7, 8, and 10, showed that both malignancies shared a clonal TCR-γ rearrangement consisting of two clearly defined fragments of 215 and 219 base pairs (bp). These fragments were accompanied by a slight polyclonal background probably due to reactive bystander cells **(Figure 13 A-C)**. The identical fragment length indicated a bi-allelic rearrangement in each lesion. Controls were carried out with DNA from reactive tonsils of healthy individuals, which lacked this characteristic bi-allelic rearrangement and showed an expected polyclonal reaction. Additionally, fragment analysis using the degenerated oligonucleotide mix vb/JG1.1-JG1.3, designed for amplification of TCR-γ V-segments 9 and 11, yielded polyclonal reactive fragments in T-ALL and to a lesser extent in JXG DNA.

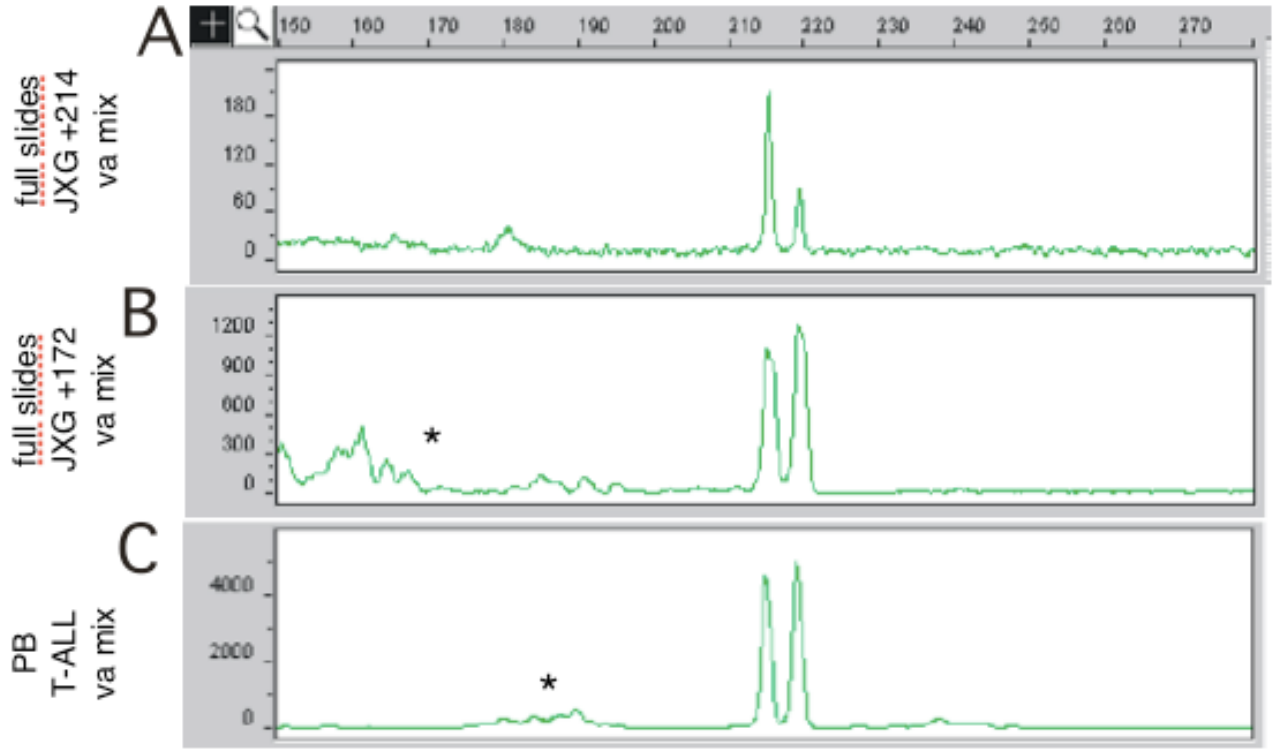

Figure 13. A) Fragment analysis of the biopsy of relapsed JXG (JXG +214) performed with va oligonucleotide mix/JG1.1-JG1.3. **B)** Fragment analysis of the biopsy of initial JXG (JXG +172) performed with va oligonucleotide mix/JG1.1-JG1.3. **C)** Fragment analysis of DNA from patients' enriched peripheral blood leukocytes (PB T-ALL) taken at the date of diagnosis, amplified with va/JG1.1-JG1.3 mix. The electropherogram shows the amplified fragments present in the T-ALL component. Both lesions, +172 JXG and +214 JXG as well as T-ALL show two identical dominant peaks of 215 and 219 base pairs (bp).

(*) Denotes a polyclonal background caused by accompanying T-helper cells.

(Performed by Dr. rer. nat. Monika Szczepanowski, Institute of Pathology, University Hospital Schleswig-Holstein, Kiel)

To rule out that contaminating remnants of the T-ALL or tumor infiltrating reactive T-cells within the JXG might have been the source of the dominant fragments, we repeated the fragment analysis using a cell pool of micro-dissected JXG cells collected carefully from the +214 JXG biopsy after CD3 staining **(Figure 14 A,B).** The same clonal bi-allelic TCR-γ rearrangement consisting of 2 fragments of 215 and 219 bp was detected in DNA

extracted from the full sections JXG lymph node biopsies, the micro-dissected JXG cells and from T-ALL blasts.

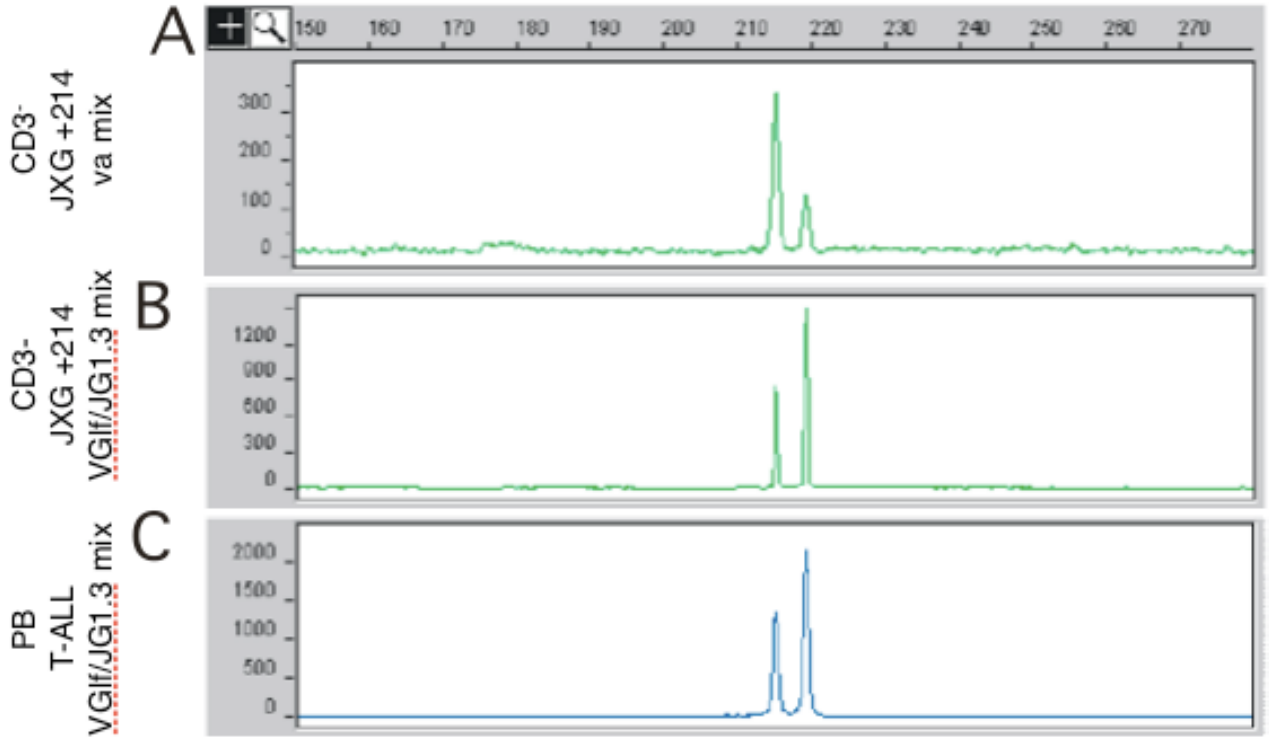

Figure 14. A) Denotes fragment analysis of laser assisted micro-dissected CD3-negative histiocytes from the +214 JXG amplified with the va mix/JG1.3 showing two dominant fragments of 215 and 219 base pairs.

B) The more specific VGIf/JG1.3 oligonucleotide mix revealed the same fragments.

C) The same fragments in the T-ALL component were amplified with the VGIf/JG1.3 mix.

(Performed by Dr. rer. nat. Monika Szczepanowski, Institute of Pathology, University Hospital Schleswig-Holstein, Kiel)

Sequence analysis of the patient specific joining regions (N regions) (University Hospital Schleswig-Holstein, Institute of Pathology, Kiel)

To reduce the sources of reactive background products that could interfere with sequencing approaches, we identified the BIOMED-2 primers which would favor the TCR-y rearrangement detected in T-ALL and JXG. The degenerated oligonucleotide VGlf (a component of va mix) and JG1.3 efficiently amplified the rearranged alleles, whereas all other oligonucleotide combinations in va and vb mixes led to polyclonal background products or synthesized no product at all confirming the specificity of the primer combination VGlf/JG1.3 for the detected TCR-y rearrangement. Micro-dissecting JXG-cells further diminished the the bulk of interfering TCR-y rearrangements attributed to reactive T-cells **(Figure 14 B)**. Again, only VGlf and JG1.3 primers amplified the rearranged alleles of 215 and 219 bp in microdissected JXG-cells, proving the specificity of these oligonucleotides for the bi-allelic TCR-γ rearrangement. These fragments were afterwards cloned and sequenced. **(Figure 15)**

Examination of 20 analyzable clones from micro-dissected JXG material revealed 10 clones with the rearranged allele TRGV8-J1/2 corresponding to the 215 bp fragment, which contained the patient specific segment VJ joining (N region) sequence 5´-CCGAT-3´. Eight clones had the rearranged allele TRGV2-JG1/2 with the patient specific N region sequence 5´-GGTCTAGCA-3´. corresponding to the 219 bp fragment. The remaining 2 clones harbored unrelated reactive T-cell rearrangements. Similarly, of the 26 analyzable T-ALL clones, 7 showed the TRGV8-J1/2 rearrangement and 14 showed the TRGV2-JG1/2 rearrangement. The rearrangements detected in the T-ALL clones were identical to the patient specific N region sequences found in the micro-dissected JXG cells **(Figure**

15). The remaining 5 clones consisted of reactive rearrangements, which were unrelated among each other.(Data not shown)

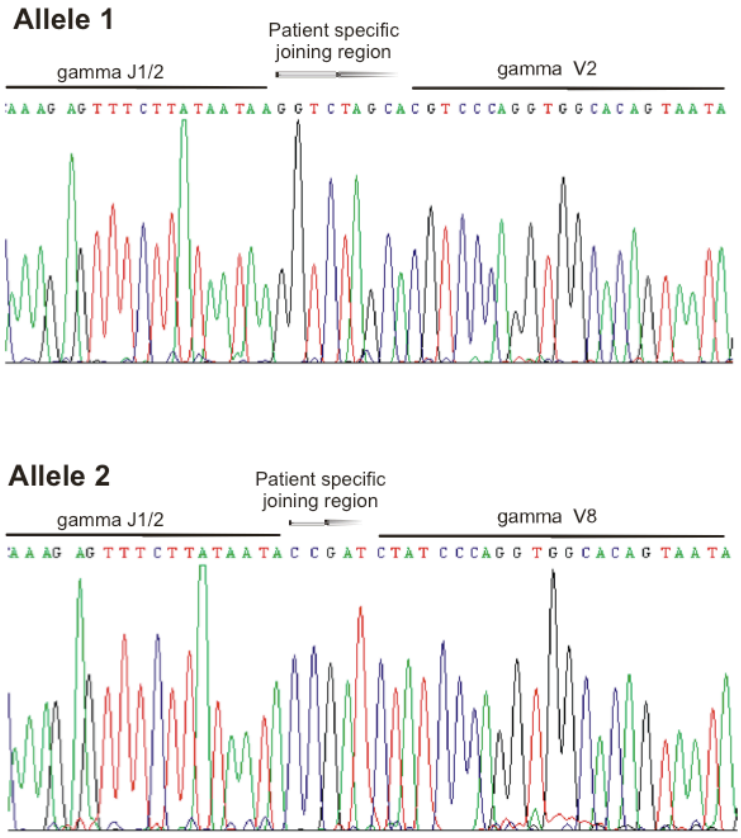

Figure 15. Automated sequencing of repeatedly sub-cloned PCR products revealed that a bi-allelic rearrangement TRGV2-JG1/2 and TRGV8-JG1/2 occurred in both lesions. The patient VJ joining sequences (N regions) 5´-GGTCTAGCA-3´ and 5´-CCGAT-3´ differed in 4 base pairs in length, reflecting the fragment size difference found in the fragment analysis. (Performed by Dr. rer. nat. Monika Szczepanowski, Institute of Pathology, University Hospital Schleswig-Holstein, Kiel)

5. DISCUSSION

Studying the relationship between malignancies gives us the opportunity to study the ontogeny of cells in the human body. The unique case presented, allowed us to study the relationship between JXG and the lymphoid lineage. Although JXG is currently classified as part of the NLCH family, recent reports of children who developed JXG as a sequel to Langerhans cell histiocytosis (LCH) show that NLCH and LCH can sometimes overlap [89-91]. Thus it is not surprising that some of them also share a relationship with the lymphoid lineage.

We will first discuss an unique case that highlights this relationship. A 5 year-old girl who developed an aggressive JXG while under treatment for a T-ALL [72]. Later we will discuss this case with respect to the literature review addressing a possible relationship between the lymphoid lineage and histiocytosis.

5.1 Case report

The case we present case is exceptional for several reasons: First, the aggressive and infiltrative nature of the JXG is uncommon in children of this age group. The systemic form of this disease occurs far more frequently during the first year of life, and although it is sometimes associated with a fatal outcome [26], the overall mortality is extremely low [35,38,43,62]. Second, the development of a systemic JXG so shortly after the T-ALL is also extremely rare. Although JXG has been reported to occur in conjunction with other hematologic malignancies [44], we found no previous reports of it co-occurring with T-ALL. T-cell acute lymphoblastic leukemia is a frequent malignancy in childhood derived from maturing thymocytes at different developmental stages [92]. The earliest T-cell precursors are characterized by the lack of expression of CD4 and CD8 surface markers. During these double-negative (DN) stages, the T-cell receptor (TCR)-β gene becomes

rearranged, driving the production of intermediate single-positive cells with a surface CD4+, CD8-, SCD3 phenotype. These cells then differentiate into early double-positive (DP) (CD4 +, CD8 +) cells, at which point the TCR-α gene rearrangement occurs. The thymic T-cell developmental process ends when mature CD4 + or CD8 + single-positive cells are produced, although further T-cell differentiation occurs in the periphery upon antigen presentation [93,94]. There is a close relationship between the recognizable patterns of surface antigen expression on leukemic T-cells and the normal stages of thymocyte development [95-97]. The blasts in our patient expressed CD1a, CD2, CD4, CD7, CD8, CD45 and cyCD3; and were negative for CD13, CD14, CD15, CD33, CD41, Glyc A and cyMPO, showing characteristics of a cortical T-ALL, corresponding to intermediate T-cells. Due to the high leukocyte count (366,800/μ) the patient was classified as high risk and treatment with the according protocol was started.

Lineage ambiguity/plasticity, infidelity and promiscuity in immunophenotypically complex hematopoietic neoplasms are uncommon but well recognized in many tumor types including biphenotypic acute leukemias [7]. The possibility that our patient initially presented with a biphenotypic or a mixed-lineage leukemia seems very unlikely, since the T-ALL lacked characteristic myeloid markers and the JXG cells presented with no lymphoid markers.

5.2 Systematic literature review

Analyzing the case reports identified in literature we found a predominance of B-cell related primary malignancies compared to T-cell related primary malignancies. This may be due to the fact that B-cell related leukemias/lymphomas occur more frequently than T-cell related ones in the general population [98]. Interestingly, the secondary histiocytosis

associated with each type of lymphoid malignancy varied between groups. The most frequent secondary neoplasm related with B-cell related primary malignancies was Histiocytic/Dendritic cell sarcoma, with atypical histiocytosis being the second most frequent one and LCH being the less frequent one. In contrast the most frequent form of secondary histiocytosis in T-cell related malignancies was LCH, with Histiocytic/Dendritic cell sarcoma being the less frequent. This observation is consistent with two recent publications by Chen et al [7,8]. In 2009 and 2010 they described a high frequency of clonal rearranged IgH in sporadic H/DC sarcomas, providing evidence that a proportion of these tumors had B-cell genotypes. Analyzing 25 sporadic H/DC sarcomas with no previous or following leukemia they found that 50% of these tumors inherited critical genetic signatures of B-lymphocytes which supports the hypothesis that these sarcomas originally might have derived from committed B-cell progenitors. In a second article Chen et al [8] analyzed 46 cases of sporadic LCH for IgH, IgK or TCR-γ. They found that 30% had clonal rearrangements, showing that a proportion of the cases had lymphoid signatures. Despite having these genetic markers, none of the LCH showed TCR α/β protein or membrane CD3 suggesting a complete lack of a functional T-cell receptor. One case even had rearrangements in both TCR-γ and IgH genes, which suggest great plasticity of these cells or great lineage infidelity. These articles, together with our findings suggest that a relationship between the B-cell lineage and H/DC sarcomas and between the T-cell lineage and LCH exist.

Another interesting difference between groups of B-cell and T-cell related primary malignancies, was the age of onset of the primary tumor. While B-cell related primary malignancies had an average age of onset of 42,8 years, T-cell related primary malignancies had a average age onset of 6 years. Also the interval between first and second neoplasms differed between groups. The median time between diagnosis of the

primary hematologic malignancy and secondary histiocytosis in the B-cell related group was 0,5 years compared to 1,41 years in the T-cell related group. Thus it appears that secondary histiocytosis related to primary B-cell malignancies appear in a somewhat shorter interval than in primary T-cell malignancies, but due to the heterogeneity of the cases and the lack of statistical power it is difficult to compare the two groups.

In summary B-cell related secondary histiocytosis appeared faster and belonged to the group of malignant histiocytosis suggesting a more aggressive nature compared to the group of T-cell related secondary histiocytosis.

The idea of a clonal relationship between the lymphoid lineage and histiocytosis is not new, we now describe it from a chronologic perspective. In 1991 van der Kwast et al. were the first to search for a clonal relationship between a malignant histiocytosis and a preceding T-ALL. Unfortunately they had no material from the primary neoplasm (T-NHL), and could only perform rearrangement analysis on the pleural effusion obtained after radiotherapy. They found the same rearranged immunoglobulin heavy chain (IgH) from the pleural effusion and the secondary neoplasm, a malignant histiocytosis. This lead them to the conclusion that the malignant histiocytosis was present at the time of diagnosis [75].

Egeler et al., described 12 cases with a co-occurrence of LCH and ALL. In 7 cases the leukemia preceded the appearance of the LCH. Six of these patients presented themselves with disseminated forms of LCH. Since all patients were receiving chemotherapy when the LCH was diagnosed, the authors speculated that therapy-induced immunosuppression played a role in the evolution of the LCH. No molecular analysis was performed in the cases [31].

In 1999, Wu et al were the first to describe a clonal relation between dendritic cell proliferations and B-cell NHL in 2 separate patients by sequencing the (X-linked) human androgen receptor (HUMARA) gene [87]. In 2001 Bouabdallah et al described a 19-year-old male who presented a true histiocytic lymphoma 4 years after the diagnosis of a B-ALL. They found that both malignancies shared the same IgH recombination, and suggested that chemotherapy played a role in the transformation of lymphoblastic immature cells into mature histiocytic ones [99]. One year later in 2002, Magni et al described a LCH occurring simultaneously with a B-cell NHL showing identical IgH rearrangements. The authors were the first to suggest a common precursor cell for both malignancies [88].

In 2004, Feldman et al described a 14 year-old-male who presented with a histiocytic sarcoma while under maintenance chemotherapy for a pre B-ALL. Both malignancies showed identical IgH and TCR-γ gene rearrangement suggesting a common clonal origin of the cells. They mention three possible mechanisms that could explain their findings. First, pre B-ALL cells may have undergone lineage switching. Second, both malignancies may derive from a common abnormality in a precursor cell. Third, chemotherapy might select malignant more differentiated cells [6]. At that time it was thought, that sporadic LCH the TCR-γ is not rearranged [100]. In 2005, Feldman et al, described two cases of LCH arising in patients with T-ALL and T-lymphoblastic lymphoma that shared identical TCR-γ rearrangements [5]. Interestingly, the histology showed atypic cytological findings in the LCH. The authors concluded, that the plasticity of the hematopoietic-cell lineages seemed greater than previously thought and for the first time mention the possibility of transdifferentiation between lineages. However, recently it has been reported, that sporadic LCH may indeed have clonal rearrangements of TCR-γ, IgH and IgK, making the transdiferentation theory less likely [8]. These findings are discussed in more detail later.

In 2007, Janssen et al. described that, similar to LCH, JXG was a clonal proliferation of histiocytic/dendritic cells, proving that JXG was not a reactive process [70]. That same year Rodig et al, reported an aggressive LCH clonally related to a preceding T-ALL. Interestingly, both malignancies showed a persistent expression of NOTCH-1. NOTCH signaling regulates normal pre-T cell development and is the most common genetic abnormality in T-ALL [101]. The authors did not find NOTCH 1 expression in 24 control cases of patients with LCH.

Castro et al [102] described the clinicopathological features of histiocytic lesions following ALL. They reported 15 different patients with histiocytic lesions that included JXG, LCH, Langerhans' cell sarcoma, Rosai Dorfman disease and histiocytic sarcoma, as well as atypical histiocytic lesions that arose after an ALL. However, a molecular analysis was only performed in 7 patients. Interestingly, the patient with the most aggressive form of JXG had striking similarities to our patient. It was a 7 year old male who developed a disseminated form of JXG one year after being diagnosed with B-ALL. He survived after chemotherapy and bone marrow transplant.

In 2008, Feldman et al [4] described 8 cases of follicular lymphoma clonally related to H/DC sarcoma. The authors suggested that transdifferentiation of the follicular lymphoma to histiocytic sarcoma was taking place. They proposed a mechanism similar to the one described by Cobaleda et al. in which deletion of paired box protein 5 (PAX 5) (a transcription factor thought to be important for B-cell development) converted mature B-cells into uncommitted precursor that were able to be transformed into T-cells [103]. Feldman et al postulated that changes in the expression of transcription factors may have

led to transdifferentiation. All evaluated H/DC sarcomas were negative for PAX 5 despite genotypic evidence of B-cell derivation supporting that transdifferentiation occurred [4].

In 2010, Wang et al [104] reported two cases of follicular lymphoma that evolved into a H/DC sarcoma finding that the IgH/BCL 2 fusion gene was present in both malignancies. Since IgH/BCL2 is a genetic hallmark for follicular lymphoma, its presence in H/DC sarcoma was highly suggestive of a clonal evolution of the follicular lymphoma. Since the IgH/BCL2 fusion gene appears late in the evolution of follicular lymphoma the authors suggested that transdifferentiation from the follicular lymphoma occurred.

Recently Kumar et al, reported a H/DC sarcoma clonally related to a pre B-ALL that shared identical IgH and TCR-γ rearrangements and a homozygous deletion of cyclin-dependent kinase inhibitor (CDKN) 2A [105]. CDKN 2A is an important tumor suppressor gene associated with a variety of cancers most importantly melanoma [106]. Kumar et al postulate that the loss of this critical suppressor gene in their patient might have lead to an abnormal myelo-lymphoid precursor.

To summarize the findings from our case report and the literature review, two possible hypothesis can be generated: First, both tumors might arise from a common precursor and second, the secondary tumor may transdifferentiate from the original one. (These hypothesis are summarized in **Figure 16.**) We find the first hypothesis more likely, considering the two articles published by Chen et al [7,8]. As discussed earlier, these 2 papers show that spontaneous occurring histiocytosis frequently show lymphoid genetic signatures and strongly support the theory of a common origin of these neoplasms and lymphoid malignancies. Taking our findings into account, it would be interesting to search for lymphoid genetic signatures in sporadic JXG.

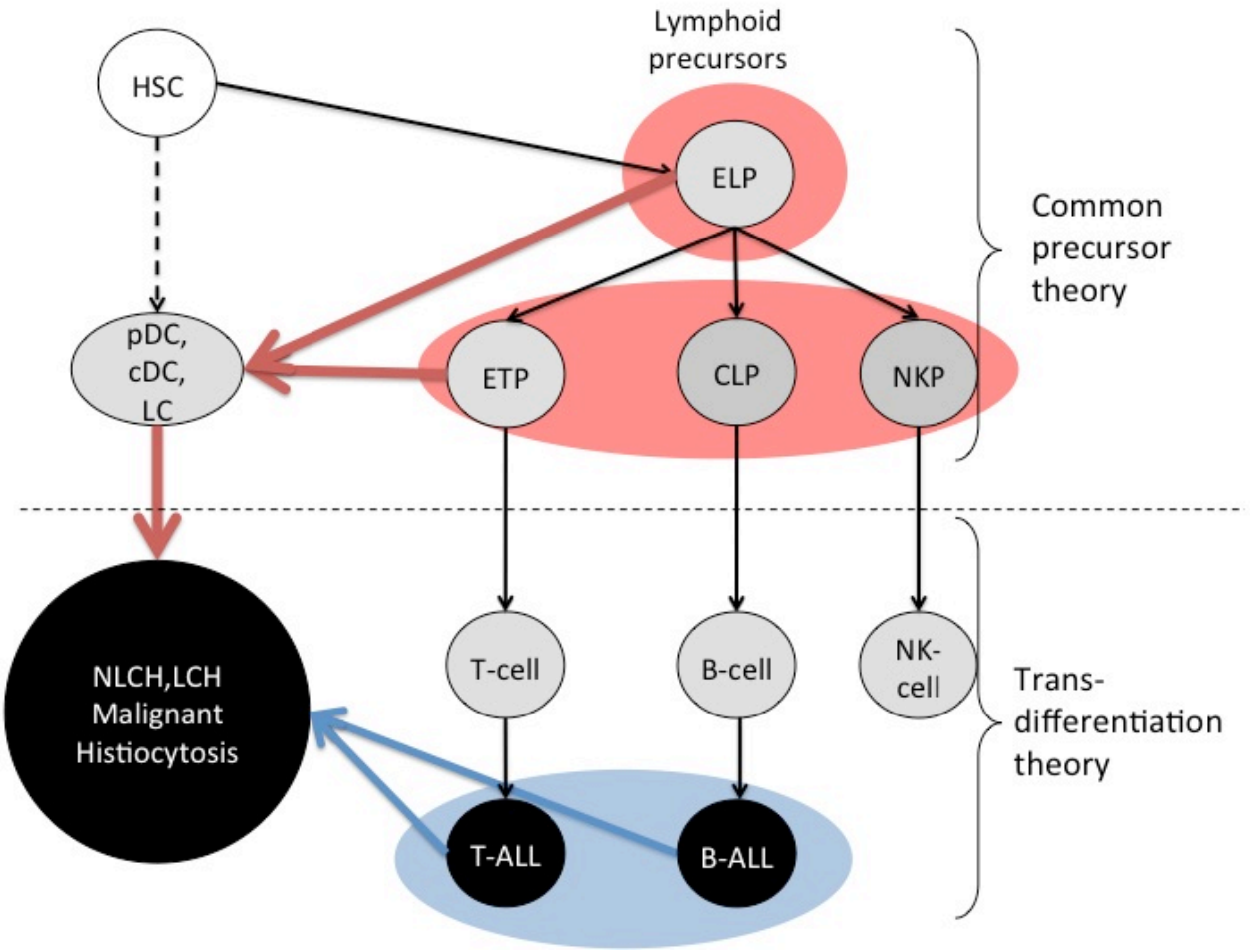

Figure 16. Model for the explanation of the relation of histiocytic malignancies and lymphoid cells. In red the common precursor theory, probably occurring early in the ontogeny. In blue a possible transdifferentiation pathway. Taken and modified from [16,107]. HSC; hematopoietic stem cell, ELP: earliest lymphoid progenitor, ETP: early T-lineage progenitor, Thym. thymocytes, CLP: common lymphoid progenitor, Pro-B: Pro B cell, NKP: Natural Killer Progenitor, INK: immature NK cell, pDC: plasmacytoid dendritic cells, cDC: conventional dendritic cells, LC: Langerhans cells. LCH: Langerhans cell histiocytosis, NLCH: non-Langerhans cell histiocytosis

The lymphoid genetic signatures in LCH and H/DC sarcoma found by Chen et al, reflect the diversity and heterogeneity of these neoplasms, and could explain the wide range of clinical manifestations we observe [7,8]. They also lead us to reconsider the current developmental model of histiocytic cells.

In 2006, Freud et al. found that NK-cells share a common origin with T-cells and DC, and retain this differentiation capacity during early stages of differentiation [108]. Earliest lymphoid progenitors (ELP) and earliest thymic progenitors for T cells (ETP), are supposed to precede other lymphoid progenitors and retain a certain myeloid differentiation potential [109,110]. Studies in mice by Anjuere and colleagues, suggest that Langerhans cells might even derive completely from the lymphoid lineage [17]. Additionally, IgH D-J rearrangements, an attribute of lymphoid lineage, have been found in mice-derived plasmacytoid and thymic DC, supporting a lymphoid origin of these cells [111,112]. However even if there is evidence supporting the lymphoid origin of some form of histiocytosis, there is still much work to be done to better understand the ontogeny and pathophysiology of these group of diseases

There are some general aspects one has to consider when drawing conclusion from a systematic literature review. Some possible bias are the small patient number and the overrepresentation of cases contributed by the large case series like those from Castro and Feldman [4,102]. It is also important to consider, that the clonal relationship between histiocytosis and lymphoid malignancies is probably more frequent than we think, since the association between LCH and acute leukemia appearing in the same individual appears to be relatively common [31] and in most cases no molecular analysis is done [102].

6. CONCLUSIONS

In conclusion, we found a relationship between a pathological differentiation within the lymphoid lineage and the pathogenesis of histiocytosis, particularly between T-ALL and a systemic form of JXG. Due to the highly malignant behavior of this form of JXG, further work-up is needed for patients affected with these diseases to optimize diagnosis and

treatment. Even if it is difficult to make associations between tumor biology and normal lymphopoiesis, our findings may suggest a common precursor cell for both diseases.

Analyzing the published cases of lymphoid malignancies related to histiocytosis, we found a grater number of case reports of B-cell related primary malignancies compared to T-cell related primary malignancies. We also found that the distribution of secondary histiocytosis between groups vary. The group of B-cell related primary malignancies had more cases of malignant histiocytosis (H/DC sarcoma) which appeared in a shorter time interval (median 0,5 years) compared to the group of T-cell related primary malignancies were the most frequent secondary histiocytosis was LCH. The interval between diseases in the later group was also longer (medias 1,4 years). The age distribution between groups also differed. The group of T-cell related primary malignancies had a younger age of onset compared to the group of B-cell related primary malignancies. The reduced number of case reports makes it difficult to draw conclusions. However, it appears that some forms of histiocytosis are related to the lymphoid lineage. Further work-up is needed to better understand this relationship and the pathogenesis of histiocytosis.

7. ACKNOWLEDGMENTS

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11. ANNEX

11.1 Presentations and Publications of this Case

This case has been presented and published as follows:

- Co-occurence of T-ALL and Juvenile Xanthogranuloma (JXG): Evidence for a common precursor? Niehues T, Leuschner I, Gokel J, Imschweiler T. 72 Wissenschafltiche Halbjahrestagung der Gesellschaft für Pädiatrische Onkologie und Hämatologie Nov 2008.

- Mädchen 5 J. mit T-Zell-Leukämie, Imschweiler T. Symposium 40 Jahre Kinder Onkologie Krefeld Dez 2008:

- Evidence for a common precursor in T-ALL and Juvenile Xanthogranuloma (JXG), Perez Becker R, Niehues T, Szczepanowski M, Klapper W. 74. Wissenschaftliche Halbjahrestagung der Gesellschaft für Pädiatrische Onkologie und Hämatologie Nov 2009

- Clonal relationship between histiocytosis and the lymphoid lineage. Case report and review of the literature. R. Perez-Becker, M. Szczepanowski, I. Leuschner, G. Janka, M. Gokel, T. Imschweiler, S. Volpel, T. Niehues, and W. Klapper 28. Annual Meeting of the Arbeitsgemeinschaft für pediatrische Immunologie (API)

- Perez-Becker R, Szczepanowski M, Leuschner I, Janka G, Gokel M, Imschweiler T, Völpel S, Niehues T, Klapper W An aggressive systemic juvenile xanthogranuloma clonally related to a preceding T-cell acute lymphoblastic leukemia. Pediatr Blood Cancer. 2011 May;56(5):859-62. [72].

11.2 Eidesstattliche Versicherung

Ich versichere an Eides statt, dass die Dissertation selbstständig und ohne unzulässige fremde Hilfe erstellt worden ist und die hier vorgelegte Dissertation nicht von einer anderen Medizinischen Fakultät abgelehnt worden ist.

Ruy Avadoro Perez