Diplomarbeit

A CASE REPORT OF A PATIENT PRESENTING WITH ACUTE RENAL FAILURE SUFFERING FROM THE RARE HISTIOCYTIC NEOPLASM OF ERDHEIM-CHESTER DISEASE

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Abbreviations

ACS	acute coronary syndrome
BGA	Blood gas analysis
BRAF	gene encoding B-Raf
CMP	Cardiomyopathy
CNS	Central nervous system
CRP	C-reactive protein
CT	Computed tomography
DDx	Differential diagnosis
DLCO	diffusing capacity of the lung for carbon monoxide
ECD	Erdheim-Chester Disease
ECH	Erdheim-Chester Histiocytosis
EDP	end-diastolic pressure
EF	Ejection fraction
FDA	Food and Drug Administration
FDG	Fluordesoxyglucose
G-CSF	granulocyte-colony stimulating factor
GM-CSF	granulocyte-macrophage CSF
HCC	hepatocellular carcinoma
HR-CT	high-resolution computed tomography
IFN-α	Interferon-α
IL	Interleukin
JJ	Double J ureteral splint
LAD	left anterior descending artery
MAPK	mitogen-activated protein kinase
MINS	Mitral valve insufficiency
MRI	Magnetic resonance imaging
NSOI	non-specific orbital inflammation
NYHA	New York Heart Association
PEG	Polyethlene glycol
PET-CT	Positron emission tomography-CT
PTH	Parathyroid Hormone
RCA	right Coronary Artery
RCX	Ramus circumflexus
SCF	stem cell factor
TEE	transesophageal echocardiography
TNF-α	Tumour necrosis factor-α
TP	total protein
TRINS	Tricuspid valve insufficiency

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Zusammenfassung

ZIELSETZUNG

Ziel der vorliegenden Arbeit ist es, einerseits die äußerst spärlich publizierte Literatur zur sog. Erdheim-Chester-Krankheit - einer seltenen Multisystem-Erkrankung und nicht-Langerhans-Zell-Histiozytose mit Multiorganbeteiligung, die von der Weltgesundheitsorganisation erst 2016 zu einem histiozytären Neoplasma erklärt wurde - insbesondere im Zusammenhang mit renaler Beteiligung (70 PubMed-Einträge), zu erweitern, und andererseits herauszufinden, ob eine bestimmte Symptomenkonstellation zum Diagnosezeitpunkt dieser seltenen Krankheit sich möglicherweise als richtungsweisend für spezifische Therapieansätze erweisen könnte.

METHODEN

Für die retrospektive Datenauswertung wurden die Krankengeschichte, Diagnostik, sämtliche verfügbare Laborparameter und Therapiekonzepte eines 60-jährigen männlichen Patienten mit akutem Nierenversagen, der an dem seltenen histiozytären Neoplasma der Erdheim-Chester-Krankheit leidet, aus den elektronischen Patientenakten der Universitätklinik für Urologie der Medizinischen Universität Graz, zwischen 2010 und 2018, herangezogen. Gleichzeitig basiert diese Arbeit auf einer systematischen Literaturrecherche im Internet, welche vor allem anhand von ‚PubMed', ‚Google Scholar' sowie der Datenbank der Universitätsbibliothek der Medizinischen Universität Graz durchgeführt wurde.

ERGEBNISSE

Vorgestellt wird der seltene Fall eines 60-jährigen männlichen Patienten, welcher 5 Jahre lang an unbehandelter Polydipsie und Polyurie litt, bevor er an der Universitätsklinik für Urologie der Medizinischen Universität Graz mit bilateraler Hydronephrose und akutem Nierenversagen vorstellig geworden ist. Interessanterweise wurde der Patient bereits im November 2010 an der Universitätsklinik für Dermatologie der Medizinischen Universität Graz einer Resektion eines kleinen, rechtsseitigen Halstumors unterzogen, welcher histologisch als mögliche Langerhans-Zell-Histiozytose diagnostiziert wurde. Der Patient war bis zur Entwicklung eines Diabetes insipidus im August 2012 sowie diverser skelettaler und multipler extraskelettaler Manifestationen klinisch asymptomatisch. Dennoch dauerte es mehr als weitere 6 Jahre, bis die richtige Diagnose der Erdheim-

Chester-Krankheit sowohl histologisch als auch genetisch durch die chirurgische Entfernung von rechtsseitigen Ureterbiopsien im April 2018 bestätigt werden und eine zielgerichtete medizinische Behandlung des Patienten mit BRAF-Hemmern begonnen werden konnte.

SCHLUSSFOLGERUNG

Die Erdheim-Chester-Krankheit ist trotz ihrer Seltenheit eine wichtige (Differenzial)-Diagnose, welche mit zahlreichen – und oft unspezifischen – Symptomen, wie z.B. Knochenschmerzen, Fieber, Nachtschweiß und Müdigkeit verbunden sein kann. Für eine akkurate Diagnosestellung ist es wichtig, dass sämtliche Untersuchungen und Ergebnisse exakt dokumentiert und für alle beteiligten Therapeuten zugänglich gemacht werden, um mögliche richtungsweisende Schlussfolgerungen und Zusammenhänge finden zu können. Der vorliegende Fallbericht ist nicht zuletzt von hoher Relevanz, da er eine 8-jährige Latenz bis zur richtigen Diagnosestellung einer Krankheit eines Patienten offenbart, welcher initial an einem Schwerpunktkrankenhaus vorstellig wurde.

Abstract

OBJECTIVE

The aim of this work is on the one hand to add information to the scarce literature on the topic of Erdheim-Chester disease, a rare multisystemic disease, a non-Langerhans cell histiocytosis with multiorgan involvement, declared a histiocytic neoplasm by the World Health Organization in 2016, particulary in connection with renal involvement (70 PubMed entries), and on the other hand, to find out whether the presence of particular symptoms might be indicative of the diagnosis of this rare disease or not.

METHODS

A retrospective data assessment of a 60-year-old male patient presenting with acute renal failure, suffering from the rare histiocytic neoplasm of Erdheim-Chester disease at the Department of Urology at the Medical University of Graz – including medical history, diagnoses, laboratory data and therapy plans retrieved from electronic patient records - from 2010 to 2018, were included into this case report.

At the same time, a systematic literature review was conducted, mainly consisting of 'PubMed' and 'Google Scholar', as well as at the University Library of the Medical University of Graz.

RESULTS

The rare case of a 60-year-old male patient suffering from untreated polydipsia and polyuria for 5 years before presenting with bilateral hydronephrosis and acute renal failure at the Department of Urology of the Medical University of Graz, is reported. Importantly, the respective patient underwent a resection of a small, rightsided neck tumor as early as November 2010 at the Department of Dermatology of the Medical University of Graz, which was histologically diagnosed as a potential Langerhans-cell histiocytosis. The patient continued to be clinically asymptomatic until the development of diabetes insipidus in August 2012, as well as several skeletal and multiple extraskeletal manifestations. Nevertheless, it took more than another 6 years until the diagnosis of Erdheim-Chester disease was confirmed histologically, as well as genetically, thanks to the surgical removal of multiple rightsided ureteral biopsies in April 2018, and thus the patient was able to consecutively receive state-of-the-art medical treatment with a selective BRAF-inhibitor.

CONCLUSION

Despite its rarity, Erdheim-Chester disease represents an important (differential) diagnosis that can be associated with numerous and often unspecific symptoms, e.g. bone pain, fever, night sweats and fatigue. For a correct diagnosis of this rare disease it is paramount that all available patient evaluations, examinations and results are documented in a meticulous fashion and are made accessible for all interdisciplinary medical experts involved in the treatment of a patient, in order to be able to timely start state-of-the-art medical treatment whenever necessary.

1 Introduction

Erdheim-Chester Disease (ECD), a rare multi-systemic disease, belongs to the group of histiocytoses and is classified according to ICD-10 under D76.3: Other Histiozytoses Syndromes.

Adding information to the scarce literature on the topic of Erdheim-Chester Disease with renal involvement is paramount, moreover a potential delay between an accurate diagnosis of the disease and the beginning of appropriate treatment warrants attention in particular. In many cases, however, the appearance of certain symptoms might be able to point the way.

On the basis of the information from applied methodological research and the conclusions drawn from it, the following research questions shall therefore be investigated in this case report:

- Might the diagnosis of specific symptoms by themselves be able to point the way for Erdheim-Chester Disease?
- In what context might a neck tumor that has been histologically diagnosed as potential Langerhans cell histiocytosis be related to a multi-systemic disease, like Erdheim-Chester?

In order to be able to compare and analyse every meaningful information for the present work, secondary research in the form of an extensive literature review was additionally used to obtain the results in addition to primary research through an empirical research. This methodology might enable a holistic recording of the investigation and a more complete understanding of existing interrelationships concerning this rare disease.

The present work is therefore divided into two parts in order to gain insights both from the interpretation of original data, as well as from the secondary interpretation of already existing information available. This will be examined in the following work on the basis of a concrete case report of a patient with the diagnosis of this rare histiocytosis syndrome and systematic literature review.

For this purpose, all definitions relevant to this work are first explained in more detail in a theoretical part, as well as empirical therapy options are provided. The second part of the recent manuscript focuses on the course description of the patient.

In a third chapter of this manuscript the results of this retrospective case study are discussed. The conclusions based on the results and the discussed contents of the following chapters form the basis for the fourth and last part of this paper.

1.1 Theoretical Foundations Histiocytosis

1.1.1 Classification

Characterized by an accumulation of macrophages, dendritic-, or monocyte-derived cells in various tissues and organs of children and adults, histiocytoses represent rare disorders. More than 100 different subtypes have been acknowledged, with a broad range of clinical manifestations, presentations, and histologies (1). The clinical presentation varies from mild to life threatening, depending on the involved cell subset and organ infiltration, as well as existing comorbidities (2). Dr. Thomas Smith first described cases of histiocytosis as early as 1865 (3). Since then, the nomenclature describing histiocytic disorders has changed fundamentally to reflect their wide range of clinical manifestations and different clinical severities of some diseases with the same pathological findings (2).

For example, in a classification, published in 1987 by the Working Group of the Histiocyte Society, histiocytoses were divided into 3 groups: Langerhans-cell (LC) or non-LC-related, and malignant histiocytoses (MH) (4).

In 2016, a new classification by Emile et al. was publicly released, classifying histiocytic disorders according to various clinical, histopathological, radiological, phenotypic, genetic and/or molecular aspects, as shown in Tab. 1 (5).

L Group: Langerhans group	• LCH • ICH • ECD • Mixed LCH/ECD

C Group: cutaneous and mucocutaneous histiocytoses	• Cutaneous non -LCH: - XG family: JXG, AXG, SRH, BCH, GEH, PNH - Non-XG family: cutaneous RDD, NXG,other NOS • Cutaneous non LCH with major systemic component
R Group: Rosai-Dorfmann disease and other non-cutaneous, non-Langerhans cell histiocytoses	• Familial Rosai-Dorfman Disease (RDD) • Sporadic RDD: - Classical RDD - Extra-nodal RDD - RDD with neoplasia or immune disease - Unclassified
M Group: malignant histiocytoses	• Primary Malignant Histiocytoses • Secondary Malignant Histiocytoses (following or associated with another hematologic neoplasia) *Subtypes: Histiocytic, Interdigitating, Langerhans, Indeterminate Cell*
H Group: haemophagocytic lymphohistiocytosis and macrophage activation syndrome	• Primary HLH: Monogenic inherited conditions leading to HLH • Secondary HLH (non-Mendelian HLH) • HLH of unknown/uncertainorigin

Tab. 1 – Classification of histiocytosis. *Source: adapted from Emile et al. 2016 (1).*

LCH 'Langerhans cell histiocytosis', ICH 'indetermined cell histiocytosis', JXG 'juvenile xanthogranuloma', ECD 'Erdheim-Chester Disease', XG 'xanthogranuloma', AXG 'adult xanthogranuloma', SRH 'solitary reticulohistiocytoma', BCH 'benign cephalic histiocytosis', GEH 'generalized eruptive histiocytosis', PNH 'progressive nodular histiocytosis', RDD 'Rosai-Dorfman Disease', NXG 'necrobiotic xanthogranuloma', NOS 'not otherwise specified', XD 'xanthoma disseminatum', MRH 'multicentric reticulohistiocytosis', HLH 'hemophagocytic lymphohistiocytosis'

However, up to date, histiocytic disorders are nevertheless roughly divided into non-Langerhans cell histiocytoses and Langerhans cell histiocytoses. The name 'Langerhans cell histiocytosis' stems from its presumed derivation from the so called 'Langerhans cells', which represent specialized dendritic cells found in the skin and mucosa. In contrast, 'Non-Langerhans histiocytoses' are thought to be derived from a monocyte-macrophage lineage (6).

1.1.2 Pathogenesis

For a detailed understanding of the pathology of histiocytic disorders, it is important to know the origins, as well as the physiology of all cells involved and the underlying biology (2). Histiocytes (from the Greek histìon = tissue) are the sessile form of macrophages, a morphological term referring to tissue-resident macrophages (1). They belong to cells of either the macrophage or Langerhans cell lineages, which is important since the histiocytic disorders are characterized by the proliferation of cells of these lineages (7).

Macrophages (from the Greek 'large eaters'), dendritic cells and monocytes belong to the mononuclear phagocyte system (8). They are large ovoid cells primarily functioning to clear apoptotic cells, debris, and pathogens. On the contrary, dendritic cells are starry cells that provide antigens on major histocompatibility complex molecules and activate naive T lymphocytes (1).

Normal histiocytes have its origin from pluripotent stem cells, which can be detected in bone marrow. Being influenced by various cytokines (e.g., stem cell factor [SCF], granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF], tumour necrosis factor-alpha [TNF-α], interleukin [IL]-3, IL-4, and others), histiocytes can become committed, differentiating into certain groups of specialized cells. Committed histiocytes can mature into one of two lineages: (1) antigen-processing cells, i.e., macrophages and monocytes, or (2) antigen-presenting cells, i.e., dendritic cells, interdigitating reticulum cells, and Langerhans cells (with Langerhans cells being dendritic cells located in the epidermis). Each category of histiocytosis can be traced to reactive or neoplastic proliferation in one of these cell lineages, as shown in Fig. 1 (2).

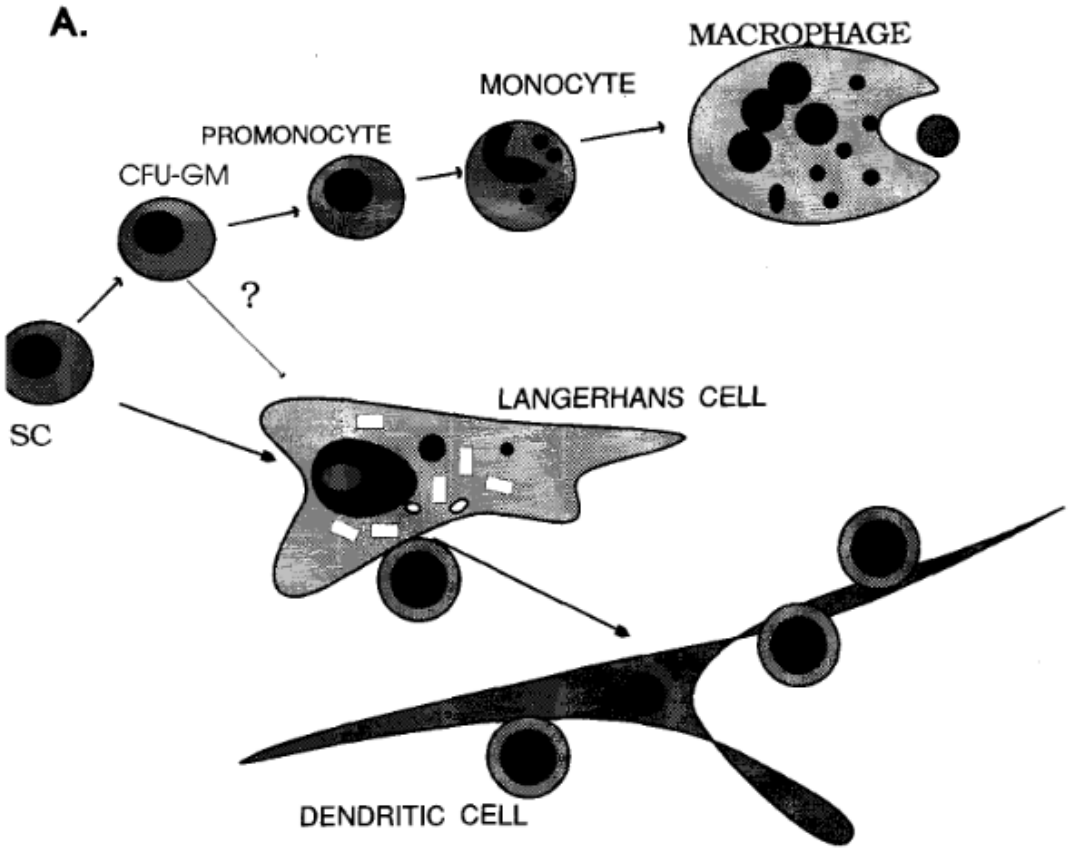


Fig. 1 – The origin of histiocytes and histiocytic disorders. *Source: Cline MJ, Blood 1994, Vol. 84, p. 2841 (7).*

The cellular origin of macrophages, Langerhans cells and dendritic cells from CD34+ stem cells (SC). Langerhans cells and, to a lesser extent, dendritic cells have distinctive intracytoplamic Birbeck granules. The direct pathway between Langerhans cells and the common granulocyte/macrophage stem cell (CFU-GM) is not certain.

1.2 Theoretical Foundations Erdheim-Chester Disease

1.2.1 Definition

Erdheim-Chester Disease (ECD) - synonyms: lipogranulomatosis, polyostotic sclerosing histiocytosis, Erdheim-Chester syndrome - represents a rare multisystemic disease, a non-Langerhans cell histiocytosis with multiorgan involvement, that was declared a histiocytic neoplasm, a slow-growing blood cancer that may originate in the bone marrow or a precursor cell (9), by the World Health Organization in 2016. It was first described by the Austrian pathologist Jakob Erdheim and the American pathologist William Chester in 1930 (10). Since then, several hundred cases worldwide of this systemic and heterogeneous disease mainly involving the bones, lungs, skin, retro-orbital tissues, central nervous system (CNS), pituitary gland, large vessels, kidneys, retroperitoneum, and heart, were reported in the medical literature (11).

This rare form of non-Langerhans cell histiocytosos is characterized by an infiltration of lipid-laden macrophages, multinucleated giant cells, an inflammatory infiltrate of lymphocytes and histiocytes in the bone marrow, and a generalised sclerosis of the long bones. As a result, various manifestations, such as skeletal involvement with bone pain, as well as extraskeletal involvement like exophthalmos, diabetes insipidus, renal impairment and CNS and/or cardiovascular involvement were observed (12).

1.2.2 Epidemiology

The exact prevalence of this disease remains unknown. More than 500 cases have been described since 1930. According to the United States Fod and Drug Administration (FDA), ECD is estimated to affect 600 to 700 patients worldwide (13). Only a very small number of juvenile cases have been reported so far (14), <15 in childhood, according to Orphanet (15). The etiology of ECD is equally still unknown, whereby reactive or neoplastic processes might build the basis of the disease (16).

Individuals affected by this disease are typically adults between their 5th and 7th decade of life with a mean age of 53 years at diagnosis (14), whereby a slight male prevalence can be observed (17). The multisystemic form of ECD is associated with a significant morbidity, which may arise due to histiocytic infiltration of critical organ systems (18). Thus, in general, patients suffering from ECD have a limited life expectancy (13).

1.2.3 Pathogenesis

Histologically, ECD is characterized by a multifocal infiltration of lipid-rich macrophages that form a network of connective tissue. The histiocytes may be positive for S100 but are negative for CD1a and have no Birbeck granulation in electron microscopy, which distinguishes Erdheim-Chester histiocytosis from Langerhans cell type histiocytosis (19).

Erdheim-Chester Disease and the related histiocytic disorder Langerhans cell histiocytosis are hematopoietic neoplasms that represent clonal proliferations of myeloid progenitor cells. This finding was shown by tracking of the BRAF V600E mutation in subsets of dendritic cells, mature monocytes, committed myeloid progenotors, and CD34+ cells of affected ECD patients. Furthermore, hematopoietic stem/progenitor cells that carry the BRAF V600E mutation can recapitulate the phenotype of ECD by differentiation *in vitro*

and in a xenograft model. Somatic mutations in components of the MAPK signaling pathway are seen in most patients with ECD. BRAF V600E is found in approximately half of all ECD cases, and mutations of this serine-threonine kinase enhances cell proliferation and survival by activating the RAS/RAF/MEK/MPAK signaling pathways. Also linked with ECD are mutations in NRAS, KRAS, ARAF, PIK3CA and MAP2K1. These findings are important since they exert implications for specific treatment modalities of ECD (6).

Understanding the aberrant cell signaling pathway involved in this disease is key, as it might allow for a more targeted therapeutic approach and the potential development of novel treatments in the future (14).

1.2.4 Diagnosis - Clinical Manifestations

The clinical presentation of patients with ECD differs depending upon the sites of organ involvement. Most patients with ECD will present with osseous involvement (s. Fig. 2) at the time of diagnosis and the great majority will show also at least one non-osseous site of organ involvement.

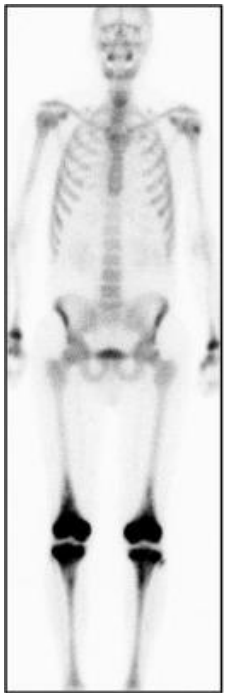


Fig. 2 – Bilateral symmetric osteosclerosis of the long bones more prominent in the lower limbs. *Source: Shah MV, Division of Hematology, Mayo Clinic Proceedings 2015, https://doi.org/10.1016/j.mayocp.2015.03.019 (20)*

Skeletal scintigraphy highlighted bilaterally symmetrical intense tracer uptake in the metaphyses and epiphyses of the long tubular bones, which is more prominent in the lower limbs.

A subset of patients is asymptomatic with bone involvement found at the time of radiography for uncorrelated conditions. In a literature review that conducted data from 259 patients with histologically proven ECD, the most common clinical presentations were bone pain (26%), neurologic features including visual disturbances (23%), diabetes insipidus from pituitary involvement (22%), and constitutional symptoms (20%) (6).

Other clinical features are cardiovascular involvement with a wide range of pathologies - including valvular abnormalities, conduction defects, fibrosis of the periaortic tissue and circumferential thickening of the aorta ('coated aorta') as shown in Figs. 3 and 4 - and retroperitoneal fibrosis ('hairy kidney'), in Figs. 4 and 5. Cardiovascular and CNS involvement are associated with the worst prognosis of ECD. The performance of a biopsy is necessary to establish a definite diagnosis with the identification of CD68+/CD1a-/S100- foamy histiocytes (17).

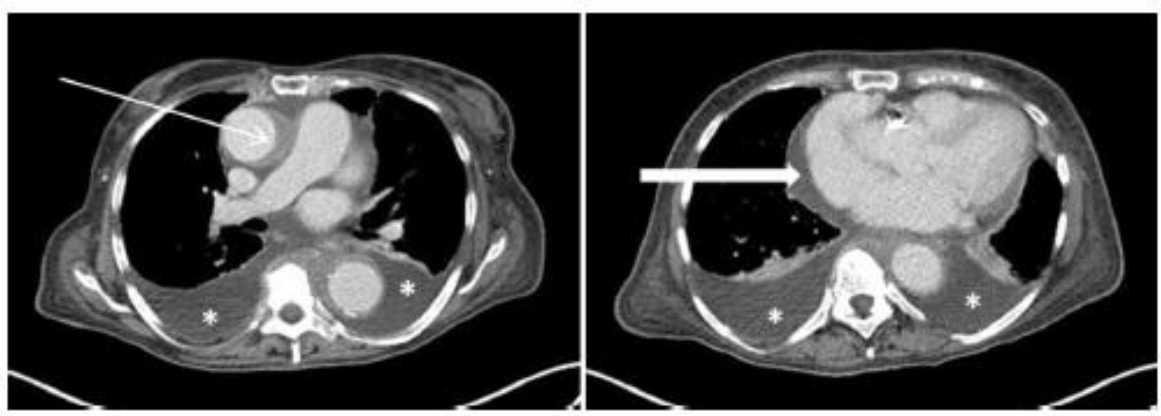


Fig. 3 – CT thorax - left image: clearly thickened aortic wall (thin arrow), right image: bilateral pleural effusions (stars) and pericardial effusion (thick arrow). *Source: Knitza J, Z Rheumatol 2018, https://doi.org/10.1007/s00393-018-0556-7, p. 67.(21)*

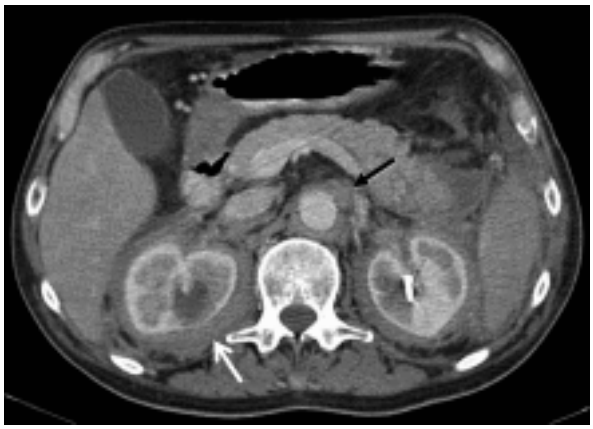


Fig. 4 – „Hairy kidneys" (white arrow) and „coated aorta" (black arrow) characteristic for Erdheim-Chester disease. *Source: Shah MV, Division of Hematology, Mayo Clinic Proceedings 2015, https://doi.org/10.1016/j.mayocp.2015.03.019 (20)*

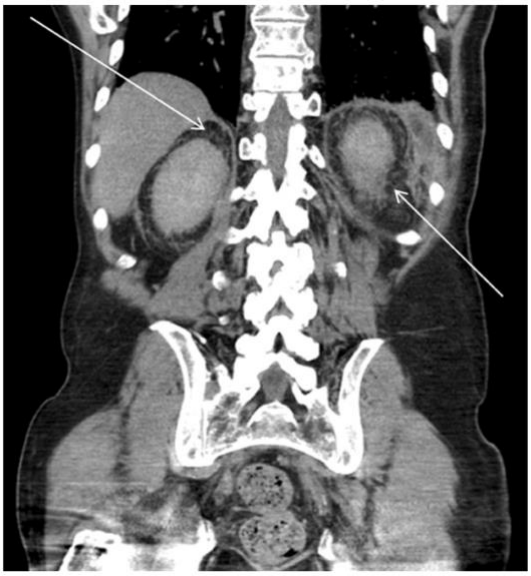


Fig. 5 – Computed tomography to show the "hairy kidneys" (arrows). *Source: Knitza J, Z Rheumatol 2018, https://doi.org/10.1007/s00393-018-0556-7, p. 69.(21)*

The diagnosis is established by clinical (medical history, as well as physical examination), laboratory, radiologic, and histologic findings. Biopsy findings include foamy-to-epithelioid macrophages, often in a fibrotic stromal background, with occasional plasma cells and lymphocytes. Macrophages test positive for CD68, CD163, and factor XIIIa and negative for CD1a and CD207, with a 20% positivity for S-100 (22).

Radiologically, orbital and systemic imaging can be useful in the diagnosis of ECD. Both, computed tomography (CT) and magnetic resonance imaging (MRI) of the orbits with contrast will reveal enhancing soft tissue-density masses in the intraconal retrobulbar space surrounding the optic nerve with obliteration of normal orbital fat. Less commonly there may be extraconal lesions present. Systemic imaging can reveal bone findings on X-ray, such as symmetric diaphysial and metaphysial sclerosis. Pulmonary findings, including dyspnea and/or cough from pleural and lung parenchymal tissue involvement, septal thickening of the lung, centrilobular nodular opacities, and interstitial opacities, might be observed. Additionally, a variety of non-specific retroperitoneal findings are almost always present, however the inferior vena cava and pelvic aspect of the ureters are typically spared (14).

The classic presentation of ocular involvement of ECD is of bilateral proptosis provoked by infiltrating orbital masses, primarly in the setting of associated periorbital xanthelasma (s. Fig. 6).

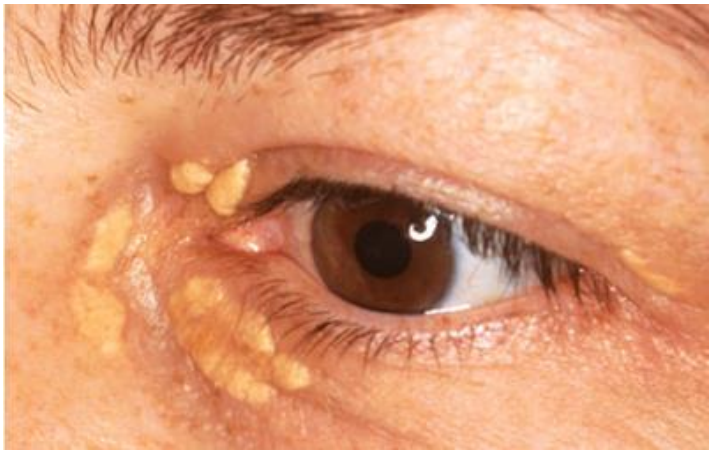


Fig. 6 – Xanthelasma. *Source: http://neues-aus-der-medizin.blogspot.com/2011/09/xanthelasmen-und-herzinfarkt-risiko.html 2019, Foto by Lößner M*

Proptosis can be severe and result in painless ophthalmoplegia and decreased visual acuity from diffuse intraconal orbital infiltration, causing compressive optic neuropathy. Besides to proptosis, other ophthalmic manifestations of ECD include xanthelasma of the eyelids, eyelid thinning, bullous chemosis, decreased visual acuity from exposure keratopathy and periorbital edema. Moreover, an ophthalmic examination can reveal optic disc edema or atrophy and retinal striae from compression, bilateral lacrimal gland enlargement, and extension of mass lesions beyond the orbital apex and skull base into the intracranial space, invading the cavernous sinus with multiple cranial nerve deficits and rarely extending further to the pituitary gland and optic chiasm. While vision loss in cases of orbital ECD occurs most commonly secondary to orbital or anterior visual pathway compression of the optic nerves, an involvement of the CNS by masses affecting the posterior visual pathways have resulted in homonymous hemianopia (14).

1.2.5 Differential Diagnoses

Due to the broad variety of symptoms, a number of differential diagnoses (DDx) can be found: histiocytosis of Langerhans cells, Rosai-Dorfman disease, Takayasu arteritis, Wegener's granulomatosis, primary hypophysitis, chronic recurrent multifocal osteomyelitis, malignant diseases, neurosarcoidosis, mycobacterial infections and metabolic disorders, to name the most common ones (15).

Retroperitoneal fibrosis, especially in connection with other systemic organ manifestations, can be a sign of ECD (16, 23). Erdheim-Chester Disease is associated with retroperitoneal fibrosis in 58% of cases (24), which can lead to a narrowing of the ureters and thus to renal

insufficiency and hydronephrosis over time. Initially, an IG4-associated disease is often considered. However, most patients present asymptomatic (21).

According to a recent report by Goldberg and colleagues, the DDx of ECD includes as well other causes of proptosis and infiltrative mass lesions of the orbit, sarcoidosis, non-specific orbital inflammation (NSOI), also known as orbital inflammatory pseudotumor, IgG4 related disease (IgG4-RD), and metastatic tumors to the orbit (14).

1.2.6 Therapy

According to Campochiaro *et al.*, Interferon-α (IFN-α) represented the established first-line treatment in ECD, since it has been clearly demonstrated to prolong overall survival. Anakinra, a genetically engineered human IL-1 receptor antagonist belonging to the group of immunosuppressants, and infliximab, a chimeric monoclonal antibody directed against the tumor necrosis factor-α (TNF-α), also known as a TNF-α blocker, have also led to encouraging results and should be taken into consideration when treatment with IFN-α fails. More recently, the BRAF-inhibitor vemurafenib has been used in small groups of ECD patients with optimal efficacy in all treated cases. Nevertheless, its adverse effects and scarce data on its long-term efficacy and safety still discourage its use as a first-line treatment option. Further studies are strongly needed to deepen the understanding and treatment of this often neglected and overlooked disease (17).

Vemurafenib was approved by the FDA in 2012 as monotherapy for the treatment of adult patients with *BRAF-V600* mutation-positive unresectable or metastatic melanoma. For the first time, a specific targeted therapy for malignant melanoma was thus made possible. Vemurafenib is an inhibitor of the BRAF serine threonine kinase. Mutations of the BRAF gene lead to a constitutive activation of BRAF proteins, which can trigger cell proliferation without the presence of associated growth factors.

In 2017, the FDA approved the first treatment for ECD with vemurafenib, which is indicated to treat patients whose cancer cells demonstrate the *BRAF-V600* genetic mutation. Approximately 54% of patients with ECD have the *BRAF-V600* mutation. Vemurafenib is a kinase inhibitor that functions by blocking certain enzymes that promote cell growth. It was designed to inhibit certain mutated forms of BRAF, which cause an

abnormal signaling inside cancer cells leading to tumor growth. BRAF itself represents a protein in a cell signaling pathway that helps control cell growth and survival (13).

In summary, the first-line therapy of ECD consists of the administration of IFN-α (standard or PEG conjugated) and bisphosphonates can be used to control bone pain. Patients with exophthalmos receive cladribine, which can also be used in the absence of efficacy of other treatments. In mild forms of ECD and insufficient efficacy of IFN-α, anakinra (IL-1 receptor antagonist) may relieve symptoms. Furthermore, vemurafenib (BRAF-inhibitor) and infliximab (TNF-α blocker) can be used (16).

1.2.7 Prognosis

The prognosis of ECD varies according to organ involvement. In patients with CNS manifestations the prognosis is generally the worst. Under IFN-α therapy, the mortality rate is currently 26% and the 5-year survival rate 68% (16).

The highly variable prognosis of this disease depends mainly on the extent and distribution. It reaches from asymptomatic bone lesions to multisystemic and life-threatening forms. The scientific medical literature, mainly published before the year 2000, often reports a very poor prognosis, but the treatment of ECD has improved significantly since then. Due to this improvememnt, mortality rates have considerably decreased over the last years. It is important to understand that due to the natural course of the disease there are many ECD patients who are able to maintain a high quality of life for decades. However, effective treatment options and regular monitoring of these patients is required (25).

2 Materials and Methods

A systematic literature review was conducted on the Internet, mainly in ‘PubMed’ and ‘Google scholar’, as well as at the University Library of the Medical University of Graz. These findings were compared with the results of the presented case from retrospective data assessment retrieved from electronic patient records - in the period from 2010 to 2018 - at the Department of Urology of the Medical University of Graz.

For the literature review, 'MEDLINE' and 'PubMed database' were searched with the terms:

- erdheim-chester disease AND acute renal failure;
- ((erdheim[tw] AND chester[tw]) OR Erdheim-Chester[tw]) AND retroperiton*[tw] AND (fibrosis*[tw] or fibrot*[tw])

This study was approved by the ethics committee of the Medical University of Graz (31-223 ex 18/19).

3 Results

3.1 Case Report

3.1.1 General Information

Besides an introduction to the complex diagnostic field of ECD, this manuscript reports a rare case of a 60-year-old male patient who suffered from untreated polydipsia and polyuria for 5 years before presenting with bilateral hydronephrosis and acute renal failure at the Department of Urology of the Medical University of Graz. Interestingly, the respective patient underwent a resection of a small, rightsided neck tumor as early as November 2010 at the Department of Dermatology of the Medical University of Graz, which was histologically diagnosed as a potential Langerhans cell histiocytosis. The patient continued to be clinically asymptomatic until the sudden development of diabetes insipidus in August 2012, as well as skeletal and multiple extraskeletal manifestations. Nevertheless, it took more than another 6 years until the diagnosis of ECD was confirmed histologically, as well as genetically, thanks to the surgically open removal of rightsided ureteral biopsies in April 2018, and thus the patient was able to receive consecutively a state-of-the-art medical treatment with the BRAF-inhibitor vemurafenib.

3.1.2 Retrospective Data Assessment

Due to increasing polydipsia and polyuria at the end of September 2017, the respective patient, born in 1959, visited a specialist of internal medicine. A detailed examination of the patient was carried out and demonstrated:

- ECG: left ventricle repolarisation malfunction;

- Sonography of the abdomen: right kidney: confluent cyst DDx Hydronephrosis, left kidney: 2 cortical cysts;
- Sonography of the carotid and of the thyroid gland: findings inconspicuous;
- Ultrasound cardiogram: left hypertrophy, diastolic dysfunction, MINS II-III, TRINS I;
- thorax X-ray: interstitial changes, presumption of interstitial pneumonia;
- CT-Thorax: interstitial changes, no neoplasia

Polydipsia and polyuria have (mildly) bothered the patient since September 2012, so far without any further clarification or therapy. Kidney cysts on the right were diagnosed in 2010, since then the patient was under observance at the specialist of internal medicine. A Langerhans tumor (neck; histology: ruptured epidermal cyst with extensive granulomatous inflammatory reaction with proliferation of Langerhans cells, partly in dense aggregates) was surgically removed in 2010. For years the patient complained about a significant fatigue, which has increased over time. Thoracic pressure pain had existed two times when performing sports activities. The body weight of the patient was stable over time. No allergies were known except hay fever. The medications so far were: Pantoprazole (reflux symptoms), Asprin, Clarityn (hay fever). Pre-existing conditions: hay fever, kidney cysts, spinal canal stenosis, Langerhans tumor neck (ex 2010).

HR-CT of the thorax, 28th of September 2017

Extensive reticular interstitial lung changes with subpleural thickened interlobular septa. The thickening of the septa smooth, no nodular septal thickening. Significantly thickened interlobular septa in both lungs, especially subpleural in both upper lobes. In addition, frost-like blurred contours of the centrilobular shadows around the bronchioles, more accentuated in both upper lung lobes, partly also nodular centrilobular structures. The bronchial tubes are normal. Overinflated lobules and scar distraction in both upper lobes. In the mediastinum individual small lymph nodes, the largest (azygos lymph node) with 1.6 x 1cm. Minor ectasia of the ascending aorta with 4cm in diameter, minor calcifications in the left coronary artery. Moderate pleural effusions on both sides. Encapsulated slightly increased fluid accumulation with a depth of up to 8mm ventral the Cavum pericardii, otherwise the pericardium inconspicuous.

Interpretation of the results (HR-CT of the thorax):

Interstitial changes of the lung with centrilobular shading of the upper lobe and smooth, limited thickened interlobular septa. In view of the long history of an allergy, subacute hypersensitivity pneumonitis should be considered. The pleural effusions and the thickened interlobular septa may be related to interstitial edema. The lung changes can only be accurately assessed in combination with clinical or laboratory data (DDx: eosinophilia). The heart size appears in the CT in the normal range. No clear indication of cardiac genesis of the pleural effusions and interstitial edema. Small encapsulated pericardial effusion ventral. Secondary finding: only partially reproduced cystic structures in the sinus renalis (parapelvine cysts and/or urinary stasis in question).

To enable a further diagnostic clarification, the patient was referred to the Department of Internal Madicine at Barmherzige Brüder (BHB) Hospital Graz.

Hospitalisation at Barmherzige Brüder (BHB) Hospital Graz, end of September 2017

Investigations:

- CT: hydronephrosis IV left, hydronephrosis II-III right, perirenal stranding both sides
- TEE: morphologically inconspicuous left ventricle with limited function, low-grade MINS

- Ultrasound cardiogram: marginally large left ventricle, high degree of functional impairment with 30% EF, diffuse hypokinesia of all wall sections (suspected St.p. myocarditis)

A stress MRI examination was recommended.

Afterwards the patient was transferred from BHB Hospital Graz to the Department of Urology of the Medical University of Graz, because postrenal kidney failure was suspected.

Hospitalisation at the Department of Urology of the Medical University of Graz, 5th - 6th of October 2017, due to further clarification

Summarised medical history: heart failure III-IV° detected at the BHB Hospital Graz; Mitral failure II-II°, presumption of coronary heart disease; St.p. permanent stenocardia;

renal failure stage III - presumption of hydronephrosis on both sides; creatinine increase (3rd of October: 2.08 mg/dL; 4th of October: 2.37 mg/dL; 5th of October: 3.72 mg/dL); nicotine abuse (~ 20py); lung congestion, effusions; polyneuropathy syndrome; arterial hypertension; hyperchromic anemia.

Investigations:

Thorax two levels, 6th of October 2017

The heart shadow located in the size standard. Vessel-typically configured upper mediastinum and hilus regions. Aortic sclerosis, ectasia and elongation and no signs of acute congestion. Reinforced peribronchovascular pulmonary framework drawing. No circumscribed pneumatic infiltrate can be distinguished in the visible lung sections. Angular effusion on the right, no pleural effusion on the left. The interlobia are more strongly represented. Degenerative spinal column changes.

Internal Medicine Board, 6th of October 2017

Evaluation/Recommendation:

Cardiomyopathy (CMP) NYHA II-III (anamnestic), acute on chronic renal failure in cystic kidney, diarrhea and antibiosis according to cardiorenal syndrome, hypochromic anemia. Morning blood collection: complete serum profile, venous blood gas analysis (BGA), iron status, total protein (TP), albumine, urine including urinary cytology and albumine in urine. Further procedure depending on nephrological findings. Clinical monitoring for dyspnoea with hydrogenation. Daily weight control, spirometry. Cardiological Board for clarification of cardiac situation.

Cardiological Board, 6th of October 2017

Evaluation/recommendation:

Acute renal failure for clarification is currently clearly in the foreground, in the absence of preoperative anaesthesia examination release primarily non-invasive imaging; CMP of unclear genesis, anemia for clarification, infection of unclear genesis. In case of the exclusion of a postrenal cause, coronary angiography in the interval after recompensation, stabilisation of renal function, anemia clarification and infection remediation plan.

Renal scintigraphy, dynamic, Furosemid, 6th of October 2017

Left kidney: Inhomogeneous discretely delayed and reduced perfusion; inhomogeneous delayed onset and strongly protracted tubulo-epithelial secretion. This strongly protracted tubulo-epithelial secretion can be visualized during the entire course of the examination and remains unchanged even after diuresis stimulation; the excretion phase in this strongly delayed tubulo-epithelial secretion cannot be judged meaningfully; in any case no significant indicator urinary depot can be visualized.

Right kidney: Discretely delayed perfusion; discretely delayed onset of tubulo-epithelial secretion and further protracted protracted. In the excretion phase significantly delayed urine outflow from the middle and cranial renal pelvis with significant indicator urine depot formation. After diuresis stimulation of good responses of this indicator urine depots with almost complete emptying. Furthermore, the significantly delayed tubulo-epithelial secretion can be demonstrated, which is also responsible for the majority of the pathological curve in the computer-assisted evaluation. The side-separated relative renal function left/right is 23/77%.

In lateral comparison, severely restricted renal function on the left with reference to diffuse renoparenchymatous damage (this is illustrated by the strongly protracted tubulo-epithelial secretion); the excretion phase cannot therefore be judged meaningfully - at least no significant indicator urine depot formation.

The right kidney shows the clearly better function with diffuse renoparenchymatous damage (which is reflected in the delayed tubulo-epithelial secretion); there is also a primarily compensated urinary outflow disorder from the middle and cranial renal pelvis calyceal system. On both sides a large part of the pathological curve is due to delayed tubuloepihelial secretion in the computer-assisted evaluation.

Hospitalisation at the Department of Internal Medicine of the Medical University of Graz, Division of Rheumatology and Immunology: 6th - 25th of October 2017 – takeover from the Departement of Urology after an Internal Medicine Board due to acute on chronic kidney failure, newly occurred heart failure, polydipsia and polyuria (known since 2012).

Main diagnosis:	Postrenal renal failure
Further diagnoses:	Presumption of Langerhans cell histiocytosis
	Diabetes insipidus

Iron deficiency anaemia

Arterial hypertension

Hypergonadotropic hypogonadism

Status:

The patient presents in a good general condition and normal nutritional status. The pupils are round, medium wide, isocor; direct and indirect light reflexes are prompt and lateral, Xanthelasma on both sides under the lower eyelids, no lymph nodes at the neck are palpable.

Cor: heart tones pure, rhythmic, normocard

Pulmo: vesicular breathing sound on both sides

Abdomen: intestinal noises audible in all 4 quadrants, no pressure pain

Extremities: peripheral pulses palpable, low leg thigh edema (right > left)

Nephrological consultation, 11th of October 2017

Rather acute renal failure (PTH 70). No indication for vasculitis (immunology negative), glomerulonephritis, no proteinuria. After discontinuation of candesartan, decrease of creatinine (3.6 - > 2.5). According to scintigraphy: compensated hydronephrosis.

The findings were re-evaluated with the Departement of Urology: nephrologically, a ureter splint on the right appears to be useful, especially in the case of rather acute renal failure (PTH 70) and a broad renal parenchyma on the right side; administration of Norvasc 10 mg; high-grade iron deficiency anaemia - further gastrointestinal clarification recommended; after decrease of the inflammatory parameters parenteral iron substitution recommended.

Pulmonary function test, 11th and 16th of October 2017

The alveolar diffusion capacity is slightly limited.

CT of the thorax 13th of October 2017

In comparison to an external preliminary investigation, 5th of October 2017, tendental regression of the small-spotted and small-modular compressions bipulmonary. Progression of cystic confluent changes in the area of the upper lobe on bothe sides. In the course imaging primarily compatible with histiocytosis, further assessment and differentiation to other entities.

The observed changes are not typical for subacute hypersensitive pneumonitis. Small cystic changes up to max. 6mm diameter are emphasized by the upper lobe on both sides. Small modular interstitial lung changes are also emphasized by the upper lobe on both sides and to a lesser extent by the lower lobe. No pleural effusions. The central tracheobronchial system freely continuous. As far as natively assessable, no evidence of pathologically enlarged lymph nodes mediastinal, hilary and axillary on both sides. No pericardial effusion. Degenerative axial skeletal changes. Partially captured parenchymatous upper abdominal organs in native mode inconspicuous.

Pulmological findings, 16th of October 2017

The patient is hospitalised at the Division of Rheumatology due to acute renal failure, as well as a newly developed heart failure, anemia, suspicious interstitial lung changes and increased inflammatory parameters of unclear genesis.

The patient quit smoking about 4 weeks ago (~ 20py). He presents himself in a good general condition, apart from a stress dyspnoea according to NYHA II-III. The patient is afebril. He has been suffering from a dry cough without sputum for 3-4 months. Pre-therapy: Claritrhomycin + Clavamox for 2 weeks until 5th of October 2017. The patient reports that he has felt tired for years, whereby this condition has increased over the recent weeks. Thoracic pressure pain has existed 2 times during sports activities. The body weight is stable.

In summary of the findings (characteristic HR-CT image, cigarette smoking status, diabetes insipidus), the diagnosis might be a multifocal and multisystemic Langerhans cell histiocytosis. A bronchoscopic or surgical lung biopsy is currently not required to confirm the diagnosis. The lung function shows no obstructive/restrictive patterns, the blood gas values are satisfactory, a slight restriction of the carbon monoxide diffusion capacity is noticeable. Clinically, the patient reports NYHA II-III stress dyspnea, which may also be associated with the CMP and heart failure. On the pneumological side, no therapy extension is currently indicated. Absolute nicotine intolerance is of great importance. Further imaging with regard to lytic bone lesions, the presentation of the patient in the haematological outpatient clinic (due to multiorgan involvement) and the control of the lung function (including the diffusing capacity of the lung for carbon monoxide [DLCO]) in the outpatients clinic in 1 month is recommended.

MRI of the brain skull, 17th of October 2017

Since the administration of contrast medium because of limited kidney function is rejected by the patient, a special examination of the sella is not possible. Apart from individual punctiform marrow position lesions, the brain parenchyma is inconspicuous. Normal width of the inner and outer cerebrospinal fluid spaces. No diffusion disorder is found. No evidence of an intracerebral space requirement. In the native CT the sella is inconspicuous. Equally, no abnormalities in the area of the infundibulum are natively radiologically found. The suprasellar cistern is free. Secondary finding: A significant widening of the mucous membrane in all paranasal sinuses is observed.

Endocrinology findings, 18th of October 2017

Diabetes insipidus centralis, primarily secondary hypoparathyroidism in vitamin D deficiency, hypergonadotropic hypogonadism. In today's laboratory control, a 12-hour thirst test shows a distinctly low urinary osmolarity as well as an increased serum osmolarity. These findings correspond to diabetes insipidus centralis. Sodium in the uppermost normal range also suggests this. The vasopressin is in the lower normal range.
Recommendation: - in vitamin D deficiency - supplementation with Oleovit D3 drops, 35 drops once per week, introduction of Minirin nasal spray, 1 puff in the evening before going to sleep (if necessary further increase to max. 1-0-1). Regular electrolyte checks (especially of sodium because of the danger of hyponatremia in case of an overdose) are mandatory. Regarding the hypogonadism, we recommend observance for the time being, since symptoms are absent. A bone density measurement is recommended. A check-up in the outpatient clinic in approximatively 4-6 months is recommended.

Urological findings, 18th of October 2017

Ureteral stenosis on both sides. Continue to balance patient and control creatinine. Dysuria and low-grade macrohaematuria can be considered normal after splinting. In case of fever, shivering or insatiable pain, an immediate presentation of the patient at the Department of Urology is warranted.

Hematological findings, 19th of October 2017

For an exact diagnosis of Langerhans cell histiocytosis a biopsy of the lesion is mandatory. In the investigations undertaken so far, no evidence of lesions in the skeletal system were

found. A bone marrow biopsy does not lead to desired results. A lung biopsy might be considered.

Findings by cardiac catheter, 23rd of October 2017

Diagnoses: False positive thallium myocardial scintigraphy
Beginning coronary heart disease
Left ventricle normal size, normal pump function, End-diastolic pressure (EDP): increased
Mitral valve insufficiency Grade 0-I
Spastic vessels
Left anterior descending artery (LAD) with 30% stenosis in proximal third
Ramus circumflexus (RCX) with 30% stenosis proximal at outlet

Radionuclide angiography, soft tissue image, 25th of October 2017

Result: Inconspicuous 3-phase bone scintigraphy of the thorax

Increased soft tissue extraction, as well as in the osseous phase clearly increased tracer uptake ossary in the upper jaw beginning on both sides. In the osseous boundary of the maxillary sinus on both sides with dorsolateral emphasis, as well as in the osseous boundary of the ethmoidal sinus and reaching cranially into the osseous boundary of the right frontal sinus. This is compatible with osseous co-participation in the context of the known Langerhans histocytosis.

2-phase positive finding in the middle to distal third of the femur - on both sides, in the proximal third of the tibia - on both sides, in the distal third of the tibia - on both sides, in the distal third of the ulna and the radius - on both sides. This might be equally compatible with a co-participation in the context of the Langerhans histocytosis.

In the osseous phase elongated increased tracer uptake in the middle third of the humerus shafts on both sides, focal in the middle third of the right clavicle, in the trochanter minor on both sides as well as in the proximal femoral shaft third on the left lateral. Co-participation in the context of the underlying disease. Discretely focally increased tracer uptake in the left calcaneus - as in the onset tendinopathy of plantar aponeurosis. The observed findings are equally compatible with multifocal Langerhans histiocytosis.

Laboratory, 24th of October 2017
Creatinine: 1.6 mg/dL

Summary of the hospitalisation:
The patient was taken over by the Department of Urology with the suspicion of acute renal renal failure. In addition, a newly diagnosed heart failure, anemia, suspicious interstitial lung changes according to external thoracic CT and increased CRP of unclear genesis were present.

A nephrological consultation was obtained when acute renal failure was suspected, and a new suspicion of postrenal genesis of acute renal failure was expressed. Urethral splinting was performed on the 18th of October 2017 and a urinary tract infection occurred postinterventionally, which was treated empirically orally with antibiotics.

In the case of known anamnestic polydipsia/polyuria and suspected diabetes insipidus, on the one hand a drinking quantity protocol was drawn up and on the other hand a thirst test was carried out. A native MRI of the skull was inconspicuous within the scope of assessability. The diabetes insipidus could finally be confirmed. In this regard, an endocorinological board was obtained and a therapy with Minirin was started, which led to a significant decrease in the amount of urine and drinking water. Furthermore, the kidney values were decreasing.

In the case of an anamnestic presumption of newly occurred heart failure a myocardial scintigraphy was performed which showed circulatory disorders. In the coronary angiography, made as a follow-up intervention, an incipient coronary artery disease with stenoses of RCX and LAD (30% of the proximal third) was detected.

Since interstitial lung changes with suspected interstitial pneumonia had been described in an external thoracic CT, a pulmononological presentation and a thoracic CT follow-up were performed. In the imaging the presumption of Langerhans histiocytosis was raised. Lung changes, diabetes insipidus, positive nicotine history respectively st.p. Langerhans tumor would be compatible. A bioptic verification is not yet available. According to the results of the boards of pulmonology and haematology the performance of a biopsy is still being evaluated.

Due to the suspicion of histiocytosis, X-ray images of the long tubular bones were taken in which no osteolysis was detectable. However, in the following skeletal scintigraphy multiple tracer uptakes compatible with Langerhans histiocytosis were described.

Whilst an iron deficiency anaemia, several tests for hepatocellular carcinoma (HCC) were performed, which turned out to be negative. An iron resorption test was realised which revealed an iron resorption disorder. The patient received Venofer infusions and Aranesp s.c. several times during the course of the test. This therapy improved the red haemogram and the iron status. The antihypertensive therapy was adapted with the aim of achieving a stable and normotonic blood pressure. In addition, hypogonadotropic hypogonadism was found in climacterium virile, as well as hyperparathyroidism whilst renal insufficiency. Oleovit drops were used to treat vitamin D deficiency.

Department of Urology of the Medical University of Graz, 23rd of November 2017, follow-up appointment

Renal scintigraphy: In comparison to the preliminary examination from 6th of October 2017, an improvement of the findings could be observed. The right kidney showed an almost inconspicuous renal function in the recent examination. On the left side, the renoparenchymatous damage continues. Function left to right: 24 to 76%. *Laboratory*: Creatinine 1.06 mg/dL

Evaluation: Stenosis of the ureter on both sides with lying splint on both side (clearly improved function with ureteral splints).

17th of December 2017, follow-up appointment at the Department of Urology

Cystoscopy: Pig-tails removed on both sides *Uricult*: negative

11th of January 2018, follow-up appointment

Discussion of findings after the renal scintigraphy without splints and external laboratory control: Renal scintigraphy, 20th of November 2017 (+JJ) - function left to right: 24 to 76%. In the dynamic phase in the excretion phase, good spontaneous excretion with discrete non-significant indicator urine depot formation in the renal pelvis caliceal system. Renal scintigraphy, 3rd of January 2018 - function left to right: 23 to 77%.

Summary: In comparison to previous findings from the 20th of November 2017: slight deterioration in the left kidney; on the right side in the sense of decompensated ureteral stenosis, but without signs of renoparenchymatous damage.

Evaluation:

Decompensated ureteral stenosis on the rigtht. Significantly limited kidney function on the left (first and foremost within the framework of a ureteral stenosis left).

Procedure:

The findings were discussed with the patient and a so called 'Anderson-Hynes plastic' on the right side (surgery planned for the 27th of March 2018) was recommended.

Specialist of internal medicine 13th of March 2018 - internistic surgery suitability incl. current laboratory results:

Collected results:

Body height: 178cm, weight: 81.2kg, BMI: 25.6, waist-to-hip ratio: 1.09, blood pressure: 147/33mmHg

ECG: SR, 58, PQ 0, 14, horizontal type, trans. between V2 und V3, left ventricular repolarisation disorder with intrinsic activity and T flattening

Pulse wave propagation time normal: 10.2m

Appendicular muscle mass with an index of 6.2 kg/m2 still low

Body water: 29.6% (increased)

Laboratory results: without significant findings, but CRP increased

Inflammation parameters	
CRP (0 – 5 mg/L)	*15.5
Renal function	
CREATININE: serum (0.7 – 1.3 mg/dL)	*1.5
URIC ACID (3.5 – 7.2 mg/dL)	*8.3
Electrolytes / Minerals	
SODIUM (136 – 145 mmol/L)	143
POTASSIUM (3.5 – 5.1 mmol/L)	4.3
CALCIUM (2.10 – 2.60 mmol/L)	2.38
Liver function	
GOT (10 – 50 U/L)	11
GGT (-1 – 66 U/L)	14
Sugar metabolism	
HbA1c (4 – 6%)	5.2
Fat metabolism	
CHOLESTERINE (-1 – 200 mg/dL)	177
LDL (-1 – 160 mg/dL)	119
HDL (-1 – 5)	*5.5
CHOL/HDL-Chol (40 – 9999)	*32

TRIGLYCERIDES (-1 – 150 mg/dL)	132
LDL/HDL (-1 – 3)	2*3.7
URINE	
pH/Urine (5 – 9)	5.0
Urobilinogen/urine (0.0 – 1.0 mg/dL)	normal
Bilirubin/urine (0.10 – 1.00)	neg.
LEUCOCYTES (0 – 0 Leu/µL)	pos.
Protein/urine	neg.
Glucose	normal
Ery/haemoglobin	marginal
Nitrite	neg.
Other	
Ketone	neg.
Sediment	

Evaluation: There is no contraindication against the planned operation.

Hospitalisation at the Department of Urology of the Medical University of Graz, 5th - 11th of April 2018

Diagnosis: Hydronephrosis in ureteropelvic obstruction on the right side

Therapy:

6th of April 2018 - Explorative kidney exposure and ureterolysis

9th of April 2018 - Pig-tail placement on both sides

Histology:

Fibro-adiposous tissue with fatty tissue necroses and foam cell aggregates. No vital malignant tumor tissue. CD 68 pos.

First additional finding - 23rd of April 2018

The mutation *V600E* in exon 15 of the BRAF gene was detectable in the present test material.

Department of Internal Medicine of the Medical University of Graz - Emergency room, 26th of April 2018

After the patient took a meal (in sitting position), sudden nausea, but no vomiting and then a brief unconsciousness occured. No trauma, no unwanted stool or urine leakage were observed. The patient did not complain about dyspnoea, stenocardia, headache, hearing or vision problems. Since yesterday, a rash back left occured, meanwhile pulling forward into the left groin. Equally, pain in the lumbar spine area left pulling forward, was described.

Evaluation: suspected Herpes Zoster, St.p. collapse, Exclusion of an acute coronary syndrome (ACS)

Department of Dermatology and Venereology, 27th of April 2018 - 3rd of May 2018 - due to transfer from the Departement of Internal Medicine

Dermatological findings: grouped standing vesicles on erythematous base thoracic left

Diagnosis: Herpes Zoster Th 11/12 sinister

Summary of the clinical course:

The patient was hospitalised due to a herpes zoster along the TH 11-12 left dermatome. During the clinical examination, grouped vesicles on an erythematous ground, with discreet pain, were found. Under an antiviral therapy with Acyclovir in a kidney- and body weight-adapted dosage, supplemented by an adequate analgesic therapy and locatherapeutic measures by means of a zinc shaking mixture, the local findings were significantly improved.

With known ECD, recent kidney exposure and ureterolysis on the 6th of April 2018 and a pig-tail catheter placement on both sides on the 9th of April 2018, hypotonic blood pressure values became apparent in the course of the disease, which is why a combined blood pressure therapy had to be paused. At the patient's request, a further adjustment of the blood pressure should be carried out by a specialist of internal medicine in an outpatient private practice. The patient was released on the 3rd of May 2018 in a good general condition and improved local findings back into home care.

Ordensklinikum Linz Elisabethinen, Haemato-oncological ambulatory clinic, 9th of May 2018 - due to 2nd opinion

Summary:

A rare histiocytic disease is present, which, as described in the literature, is able to change the phenotype over time - a primarily purely cutaneous Langerhans cell histiocytosis has turned into the picture of a pronounced ECD. A BRAF mutation *V600E* was detected in the histological preparation of surgical specimens from April 2018, which is present in about 60% of patients.

Even though the patient is currently oligo- to asypmtomatic, a therapeutic indication is recommended, since a pronounced organ involvement is present and to prevent further

organ manifestations, in particular myocardial or pericardial involvement (the current compensated heart failure could also be attributable to the coronary artery disease), respectively cerebral or cerebellar involvement.

In view of the existing BRAF mutation, a BRAF-inhibitor would have to be chosen in the first step, whereby based on data of a French study group with a dosage selected for melanoma, a 50% dose of the standard dose is to be regarded as sufficient in the respective case. Nevertheless, side effects, in particular arthralgia, may occur in the course of the disease, whereby the dose may have to be adapted, or, in individual cases, the therapy may have to be stopped. Other possible side effects would be an increased occurrence of skin diseases/tumours, which is why a dermatological observance would be additionally recommended.

Thus, the recommendation is to start with vemurafenib 2 tablets in the morning and 2 tablets in the evening. The patient will start treatment under guidance of his main doctor (Specialist of Internal Medicine in Graz). The endocrinopathy should not be evaluated, it will probably not change under ongoing therapy and the patient will need his hormone replacement for the rest of his life. The interstitial lung picture will not necessarily have to improve. Here the essential step was to quit smoking, which often leads to an improvement of the picture. Furthermore, a PET-CT examination before starting treatment is recommend, since changes in the bones, especially sclerotic ones, also show an increased glucose cover rate, which might be used as a response evaluation in the course of the treatment.

In case of an intolerance towards the therapy or a progression during ongoing therapy, pegylated IFN once a week could be an alternative. If the BRAF-inhibitor therapy is well-tolerated and effective, an omission test could be carried out after one year of treatment. At this point, it is highly probable that further registry results or single center experiences will be available to support this approach. It should be noted that in the case of a progression of the disease, in addition to the heart, cerebrum and cerebellum involvement mentioned above, organs already affected may also show a progression. This would be in particular, since clinically often not quickly apparent, a further progression in the area of pituitary anterior lobe insufficiency. For this reason, the patient is advised to have the thyroid gland checked once a year and also to think of hyperprolactinemia, if one or both sides of the

breast would swell. Whether the existing testosterone deficiency requires substitution or not, has still to be clarified.

Regarding the ureteral splints on both sides, the patient is equally advised to leave those for the time being, especially since interstitial nephritis can very rarely be observed under vemurafenib and then, in the case of simultaneous splint removal, it would be difficult to evaluate whether a worsened renal function could be interpreted as an increased hydronephrosis or as a side effect of the medication. The suggestion would be to remove the ureteral splints after 4 to 6 weeks as the earliest time point.

Therapy plan:
Start of the BRAF-inhibitor therapy after chef medical approval; therapy management by the specialist of internal medicine in private practice.

Department of Urology of the Medical University of Graz, 19th of May 2018
Past history:
Histiocytic disease of mixed phenotype (Langerhans cell histiocytosis and ECD) involving skin, retroperitoneum, long bones, lungs and pituitary gland
St.p. Ureterolysis on the 6th of April 2018.

Summary:
Removal of both ureteral splints
Urine: Ery +++, Leuco +

Evaluation:
known bilateral narrow ureters in retroperitoneal fibrosis. known poor function of the left kidney.

Procedure:
A timely close control of the kidney retention parameters by the treating specialist of internal medicine is recommended. The patient should present any time if the renal retention parameters increase or fever or pain occurs. A vemurafenib therapy is planned to start in July 2018.

Specialist of internal medicine, endocrinology and nephrology, 7th of June 2018

The patient was last checked in May. In the meantime, a PET-CT was performed with the following results: In summary, infiltrates in the upper jaw, lower jaw, trochanter major, proximal and distal third of humerus shaft, femoral condyle, tibial head, and calcaneus on both sides, are detectable.

Laboratory results:

Renal function	
CREATININE: serum (0.7 – 1.3 mg/dL)	1.3
Electrolytes / Minerals	
SODIUM (136 – 145 mmol/L)	139
POTASSIUM (3.5 – 5.1 mmol/L)	4.7
CALCIUM (2.10 – 2.60 mmol/L)	2.29
Thyroid status	
TSH (0.25 – 4.04 µU/mL)	0.91
Ferrum status	
FERRUM (65 – 175 µg/dL)	*61
FERRITIN (22 – 275 ng/mL)	174
Transferritin (174 – 364 mg/dL)	188
Transferritin satiation (16 – 45 mg/dL)	23
EBK (218 – 455 µg/dL)	235
Trace Elements / Vitamins	
FOLIC ACID (3.1 – 20.5 ng/mL)	4.5
VITAMIN B12 (187 – 883 pg/mL)	257

Procedure:

The vemurafenib therapy will be started on 8th of June 2018, 2x2 tablets daily, other therapy remains same as before.

Therapy suggestions:

Candesartan 16 mg	1-0-0
Nebivolol 5 mg	0-0-1
Norvasc 5 mg	2x1
Thrombo ASS 100 mg	0-1-0
Minirin 0.1 mg	0-0-1
Vemurafenib 240 mg	2-0-2
Oleovit D3	35 drops/week (Thursday)
Erycytol 1 mg/mL ampoules	2 ampoules i.m., repetition in 1 month

A control of the renal function is scheduled for July 2018.

Specialist of internal medicine, endocrinology and nephrology, 3rd of July 2018

The patient has been taking vemurafenib 240 mg, 2-0-2, for 4 weeks now; he shows a good tolerability, except a sun sensitivity; despite using a protection factor 50+, an erythema developed mainly on the hands, otherwise no side effects are reported. The patient comes to the first control of the kidneys and blood values.

Laboratory results:

Haemogram	
LEUCOCYTES (4 – 11.2 Leu/µL)	4.9
ERYTHROCYTES (4.4 – 5.9 T/L)	4.7
HAEMOGLOBIN (130 – 178 g/dL)	141
HAEMATOCRIT (0.40 – 0.53%)	0.42
MCV (80 – 96 fL)	91
MCH (HbE) (28-33 pg)	30
MCHC (32 -36 g/dL)	33
THROMBOCYTES (140 – 400 Giga/L)	308
Differential Haemogram	
Basophilic granulocytes (0 – 2%)	1
Basophilic granulocytes abs. (0 – 0.11%)	0.05
Eosinophilic granulocytes (0 – 7%)	3
Eosinophilic granulocytes abs. (0 – 0.47%)	0.15
LYMPHOCYTES (17 – 47%)	*14
LYMPHOCYTES abs. (1.1 – 4.5%)	*0.7
Monocytes (4 – 12%)	*17
Monocytes abs. (0.2 – 0.7%)	*0.8
Neutrophils: segment (40 – 75%)	65
Neutrophils: rod abs. (1.8 – 7.0%)	3.2
Renal function	
CREATININE: serum (0.7 – 1.3 mg/dL)	*1.7
Electrolytes / Minerals	
SODIUM (136 – 145 mmol/L)	140
POTASSIUM (3.5 – 5.1 mmol/L)	4.5
CALCIUM (2.10 – 2.60 mmol/L)	2.43
Ferrum status	
FERRUM (65 – 175 µg/dL)	*55
FERRITIN (22 – 275 ng/mL)	95
Transferritin (174 – 364 mg/dL)	243
Transferritin satiation (16 – 45 mg/dL)	16
EBK (218 – 455 µg/dL)	304
Trace Elements / Vitamins	
FOLIC ACID (3.1 – 20.5 ng/mL)	5.2
VITAMIN B12 (187 – 883 pg/mL)	309
Other	
MTV (7 – 12 fL)	10.9

Evaluation:

The current laboratory findings are in the normal range, the renal function changed only slightly, with a creatinine increase from 1.5 to 1.7 mg/dL. The continuation of the previous therapy is recommended. Since a mild iron deficiency is observed, a therapy with Ferretab tablets 2 x 1 is recommended for a few weeks. The next control is scheduled in 6 to 8 weeks from now.

Specialist of internal medicine, endocrinology and nephrology, 28th of August 2018

The patient continously takes vemurafenib 240 mg, 2-0-2, with good tolerance, except the predescribed side effect of a sun sensitivity; an erythema developed especially on the forearms and face; joint pain rarely occurs, especially pain in the right wrist, as well as in the area of the right heel are described from time to time. The blood pressure during self-monitoring is systolic between 135 - 145, diastolic between 75 - 85mmHg. The patient comes to control the kidneys and blood values.

Laboratory results:

Renal function	
CREATININE: serum (0.7 – 1.3 mg/dL)	*1.7
URIC ACID (3.5 – 7.2 mg/dL)	*9.1
Electrolytes / Minerals	
SODIUM (136 – 145 mmol/L)	143
POTASSIUM (3.5 – 5.1 mmol/L)	4.4
CALCIUM (2.10 – 2.60 mmol/L)	2.48
Liver function	
GOT (10 – 50 U/L)	16
GPT (10 – 50 U/L)	16
GGT (-1 – 66 U/L)	21
Alkaline phosphatase (40 – 150 U/L)	106
LDH (125 – 250 U/L)	138
Hormonal status	
FSH (1.0 – 12.0 ng/dL)	4.2
TESTOSTERONE (2.48 – 6.74 ng/mL)	6.62
Ferrum status	
FERRUM (65 – 175 µg/dL)	*45
FERRITIN (22 – 275 ng/mL)	30
Transferritin (174 – 364 mg/dL)	283
Transferritin satiation (16 – 45 mg/dL)	*11
EBK (218 – 455 µg/dL)	354
Trace Elements / Vitamins	
FOLIC ACID (3.1 – 20.5 ng/mL)	4.9
VITAMIN B12 (187 – 883 pg/mL)	323
Other	
Parathyroid hormone (15 – 65 pg/mL)	40

Evaluation:

At the beginning of July, serum creatinine was 1.7 mg/dL, currently stable and unchanged. The findings are overall satisfactory. However, uric acid increased and the iron saturation is marginal, while testosterone and FSH, as well as parathormone are normalised. A PET-CT total-body is scheduled for September 2018 at the radiology department. The next control is scheduled in 6 to 8 weeks from now.

Specialist of internal medicine, endocrinology and nephrology, 13th of November 2018

A PET-CT total-body examination was performed showing only discrete uptakes (metabolism intramedullary in the proximal, middle and distal third of the femoral shaft on

both sides, further in the proximal and distal part of the tibia shaft on both sides, in the proximal humerus right focal, in the trochanter major femoris dextra focal). A significant improvement in the findings compared to the preliminary examination in terms of a good response to therapy can be reported. The therapy is taken as prescribed. The patient comes to control the kidneys and blood values. As side effect, the sun sensitivity is still present, whereby in the meantime an exanthema at the buttocks appeared, which presumably occurred as a result of the vemurafenib therapy.

Laboratory results:

Inflammation parameters	
BLOOD SEDIMENTATION 1h (0 – 20 mm)	*26
CRP (0 – 5 mg/L)	*10.0
Haemogram	
LEUCOCYTES (4 – 11.2 Leu/µL)	6.8
ERYTHROCYTES (4.4 – 5.9 T/L)	4.7
HAEMOGLOBIN (130 – 178 g/dL)	143
HAEMATOCRIT (0.40 – 0.53%)	0.41
MCV (80 – 96 fL)	88
MCH (HbE) (28-33 pg)	31
MCHC (32 -36 g/dL)	35
Thrombocytes (140 – 400 Giga/L)	378
Differential Haemogram	
Basophilic granulocytes (0 – 2%)	1
Basophilic granulocytes abs. (0 – 0.1%)	0.07
Eosinophilic granulocytes (0 – 7%)	2
Eosinophilic granulocytes abs. (0 – 0.47%)	0.14
LYMPHOCYTES (17 – 47%)	*11
LYMPHOCYTES abs. (1.1 – 4.5%)	*0.7
Monocytes (4 – 12%)	11
Monocytes abs. (0.2 – 0.7%)	0.7
Neutrophils: segment (40 – 75%)	75
Neutrophils: rod abs. (1.8 – 7.0%)	5.1
Renal function	
CREATININE: serum (0.7 – 1.3 mg/dL)	*1.6
URIC ACID (3.5 – 7.2 mg/dL)	6.1
Electrolytes / Minerals	
SODIUM (136 – 145 mmol/L)	*134
POTASSIUM (3.5 – 5.1 mmol/L)	4.3
CALCIUM (2.10 – 2.60 mmol/L)	2.37
Liver function	
GOT (10 – 50 U/L)	21
GGT (-1 – 66 U/L)	24
Sugar metabolism	
HbA1c (4 – 6%)	5.1
Fat metabolism	
CHOLESTERINE (-1 – 200 mg/dL)	*234
LDL (-1 – 160 mg/dL)	151
CHOL/HDL-Chol (40 – 9999)	53
HDL (-1 – 5)	4.4
TRIGLYCERIDES (-1 – 150 mg/dL)	148
LDL/HDL (-1 – 3)	2.9
Ferrum status	
FERRUM (65 – 175 µg/dL)	73
FERRITIN (22 – 275 ng/mL)	40

	Transferritin (174 – 364 mg/dL)	291
	Transferritin satiation (16 – 45 mg/dL)	18
	EBK (218 – 455 µg/dL)	364
Other		
	MTV (7 – 12 fL)	10.8

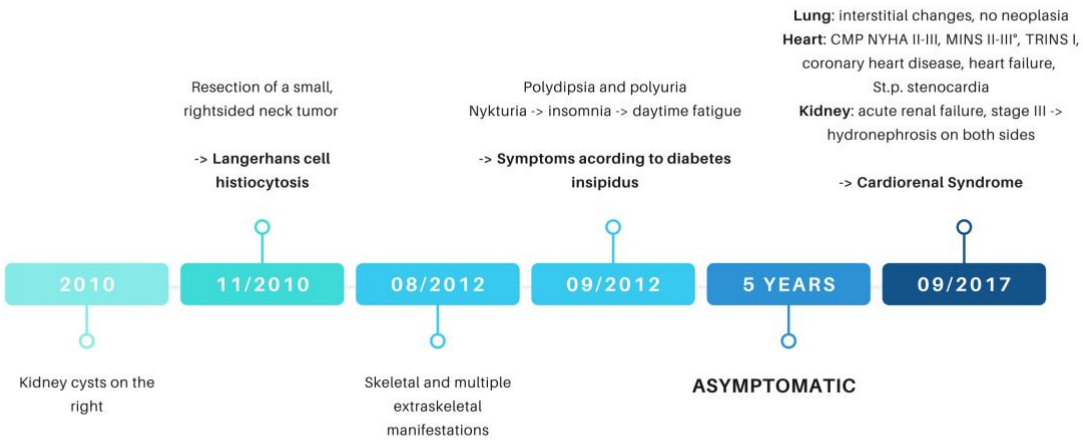
Evaluation:

The laboratory results are overall satisfactory, serum creatinine decreased slightly from 1.7 to 1.6 mg/dL compared to the last control; uric acid also normalised. A continuation of the previously established therapy is recommended.

Additional therapy suggestions:

Tardyferon 80 mg ret.	1-0-0 with lemon or orange juice
Allopurinol 300 mg	½-0-0

3.1.3 Overview



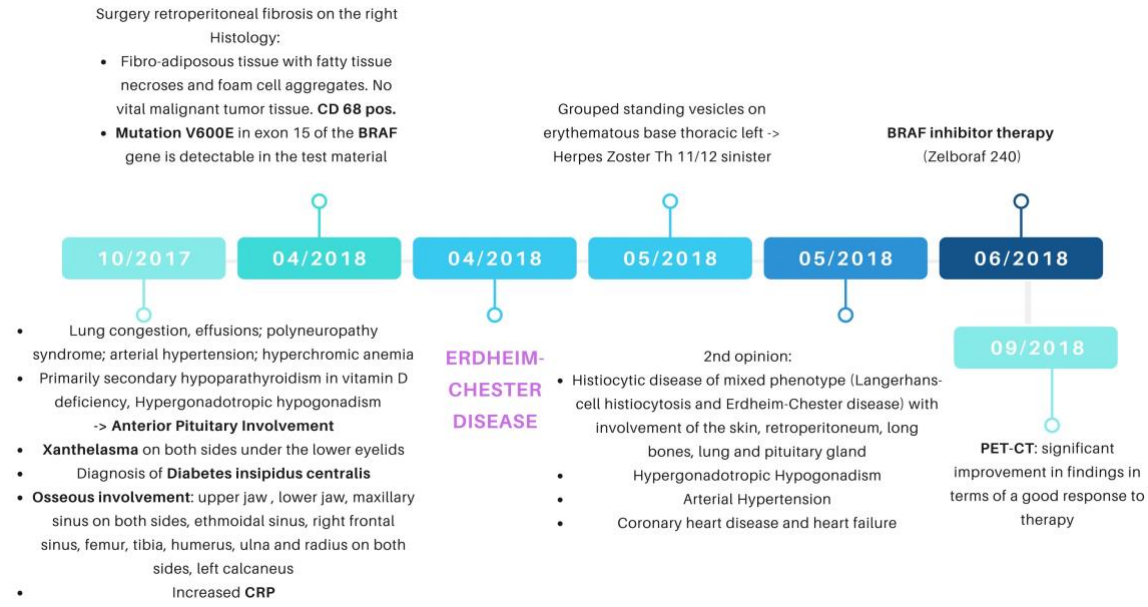


Fig. 7 – Timeline patient history

3.2 Summary of the findings

The rare case of a 60-year-old male patient presenting with acute renal failure, suffering from the rare histiocytic neoplasm of ECD with bone, cardiovascular, CNS, pituitary gland and renal involvement, is presented. The final diagnosis was based on histological, as well as immunhistochemical findings. These showed infiltrates of histiocytes and fibrosis on microscopic evaluation, as well as positive CD68 and negative CD1a on immunohistochemical stains. Additionally, the mutation *V600E* in exon 15 of the BRAF gene was detected.

Erdheim-Chester Disease represents a rare, multisystemic, $CD68^{+}$, $CD1a^{-}$, $S100^{-}$ non-Langerhans cell histiocytosis of unknown etiology with about 500 to 750 reported cases worldwide. Currently, there is no evidence for associated infectious or hereditary genetic abnormalities. Despite various clinical manifestations of ECD, respective patients almost always show a long bone involvement, such as femur, tibia, and fibula. In addition to a skeletal involvement, CNS (diabetes insipidus centralis, ataxia), retroperitoneal, renal, pulmonary, cutaneous (xanthelasma), and cardiovascular involvement have been found. Histologpathological findings are characterized by a xanthomatous infiltration of tissues by foamy histiocytes, surrounded by fibrosis and occasionally multinucleated giant or Touton cells (20, 21, 26-29).

Because 60 to 100% of ECD patients are carriers of a BRAF mutation, the disease has been recently reclassified as an inflammatory myeloid neoplasia. If no BRAF mutation is detected, the search for other ECD-associated mutations, like MAP2K1, KRAS, and NRAS, is helpful. The simultaneous presence of antinuclear autoantibodies, antineutrophil cytoplasmic autoantibodies and other autoantibodies often complicates the path to make the right diagnosis. Relatively often false diagnoses are first made, and it takes a long time before ECD is correctly identified and diagnosed (1, 21, 22, 30-32).

In this study, the bones, CNS, kidneys, retroperitoneum and the cardiovascular system were in the foreground of symptoms. Characteristic imaging findings, such as a 'coated aorta' or 'hairy kidneys' were present, as well as FDG uptakes and signal increases in both femurs and tibiae on PET-CT's and bone scans. The first symptoms in the current patient occurred at the age of 51 years, which represents the average age at symptom onset (21, 24). During disease progression, the patient developed diabetes insipidus, xanthelasmas, cardiovascular involvement, bilateral adrenal enlargement, renal impairment, interstitial lung disease, and retroperitoneal fibrosis with perirenal and ureteral obstruction on both sides. The histopathological fidings characterized by fibro-adiposous tissue with fatty tissue necroses and foam cell aggregates were found, whereby they expressed an immunoprofile of CD68+ and negative CD1a on immunohistochemical stains.

Thus, a histiocytic disease is presented, which started as primarily purely cutaneous Langerhans cell histiocytosis and turned into the picture of a pronounced ECD over time.

Variable	Langerhans cell histiocytosis	Erdheim-Chester disease
Cell of origin	Dendritic	Mononuclear-phagocyte
Population	Children	Adults
CD68	+	+
CD1a	+	-
S100	+	-
Birbeck granules	+	-
T6 protein	+	-
Bone involvement	Osteolytic/axial	Osteosclerosis/appendicular
Lung involvement	Peribronchial	Lymphangitic
Skin involvement	Common	Uncommon

Tab. 2 – Langerhans vs Non-Langerhans Cell Histiocytosis. *Source: adapted from Munoz et al. 2014 (27)*

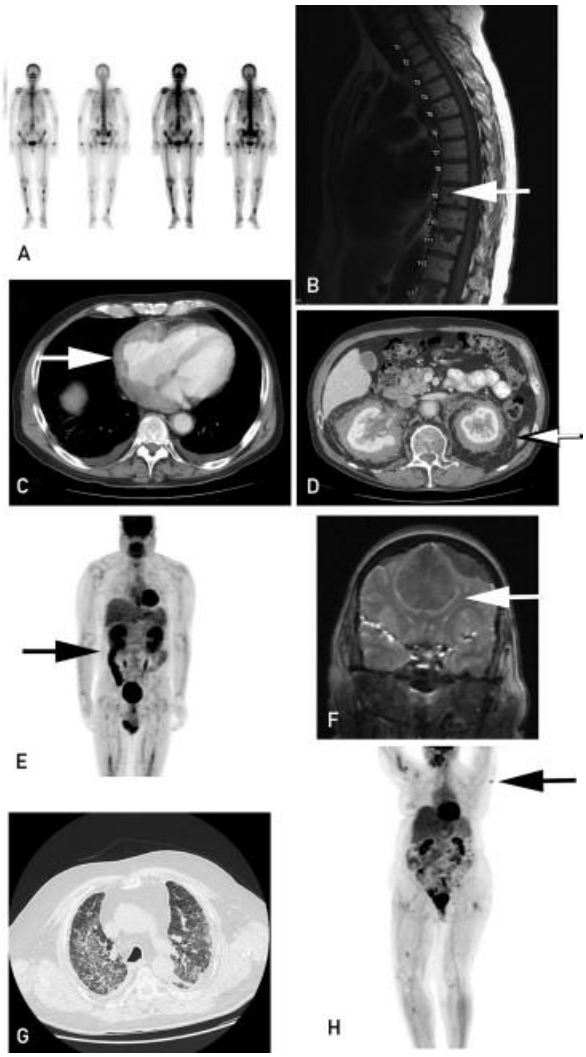


Fig. 8 – Erdheim-Chester Disease Characteristics. *Source: Munoz et al. 2014 (27)*

A. *Whole-body technetium bone scan: Erdheim-Chester disease manifested as diffuse sclerotic lesions, particularly on the diaphysis of appendicular long bones. Scattered foci of abnormal radiotracer activity were also seen, with the most conspicuous sites of abnormality in the right sacrum and bilateral tibiae and distal femora.* ***B.*** *Magnetic resonance imaging showing lesions on T9, L1, and L5 vertebral bodies with no evidence of acute compression fracture.* ***C.*** *Computed tomography of the chest showing an infiltrative mass involving the pericardium and the wall of the right atrium.* ***D.*** *Computed tomography of the abdomen showing a perirenal infiltrative mass compatible with "hairy kidney." Note the wall thickening surrounding the abdominal aorta.* ***E.*** *Positron emission tomography showing activity within the enlarged thickened kidneys and renal tissues.* ***F.*** *Magnetic resonance imaging showing dural-based masses and a central heterogeneous mass displacing the cingulate gyrus, corpus callosum, and lateral ventricles.* ***G.*** *Computed tomography of the chest showing chronic interstitial changes throughout both lungs.* ***H.*** *Positron emission tomography showing multiple hypermetabolic lesions in the subcutaneous tissues.*

No standard treatments and no known cure for ECD are established. Current therapy options include corticosteroids, IFN-α, as well as systemic chemo- and radiation therapy. However, if the pathophysiological mechanisms in a particular case are understood, a targeted therapy with vemurafenib, imatinib, and anakinra are feasible with good results (26, 33).

Previous literature has reported that ECD presenting with CNS- and cardiovascular involvement has a particularly poor prognosis (29). Fortunately, the presented patient

shows a good response to the treatment with vemurafenib, even if side effects were noticeable, namely an extreme sun sensitivity, erythemas and infrequently joint pain.

As a consequence of the presented case report, alarm bells should ring whenever a patient is diagnosed with Langerhans cell hiytiocytosis of the skin. The patient should be informed that Langerhans cell histiocytosis represents a rare disease requiring tight follow-up controls and monitoring of the course of the disease.

4 Discussion

Erdheim-Chester disease represents, despite its rarity, an important DDx. It is regarded a non-Langerhans cell histiocytic neoplasm which is accompanied by an accumulation and infiltration of various organs and tissues, e.g. of the long, mostly lower tubular bones, aortic sheathing and infiltration of further vessels, retroperitoneal fibrosis, and exophthalmos. This multisystemic disease might affect any combination of organ systems, including ophthalmic/periorbital, pulmonary, cardiovascular, renal, musculoskeletal, and CNS. Because of the diversity of organs involved, the disease is extremely heterogeneous and the presentation is often protean, because of the wide range of clinical manifestations, from asymptomatic bone-localised lesions to multiorgan infiltrations. The symptoms vary accordingly and are often non-specific, e.g. bone pain, fever, night sweats, fatigue, to name some common ones. The clinical manifestation can equally vary from diabetes insipidus, exophthalmos, xanthelasmas, cardiovascular involvement, bilateral adrenal enlargement, renal impairment, testis infiltration, interstitial lung disease to retroperitoneal fibrosis with perirenal and/or ureteral obstruction. A correlation between clinical manifestation, radiological (scans - bone, PET, MRI), and histological findings is mandatory for a correct identification of the disease (21, 28, 34, 35).

Moreover, pathology investigations are vital for a correct ECD diagnosis and proper life-saving treatments (34). The identification of associated mutations and immunohistochemical parameters can be helpful in making the diagnosis, and allows for the development and application of targeted treatments in this setting (35). Due to its versatility and many unspecific symptoms, illustrated in the overview, Figs. 9 and 10, as well as the rarity of the disease, symtoms are misinterpreted and it often might take several years until a final diagnosis is achieved. In conclusion, the presented case should hopeably contribute to a better understanding and add information to the complex field of ECD and the most commonly related questions with this rare entity.

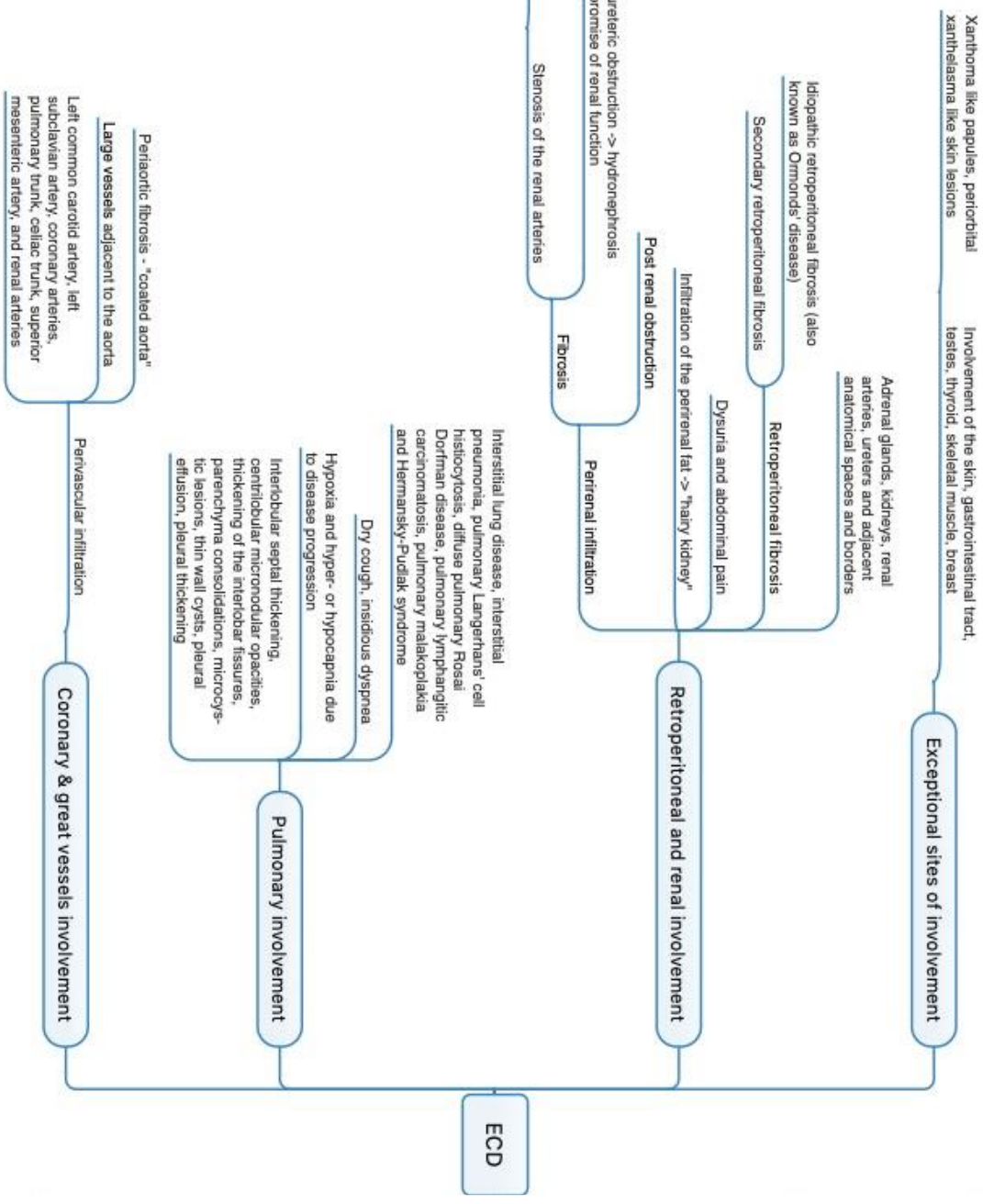


Fig. 9 – Overview ECD organ involvements and clinical manifestations, *part 1.*

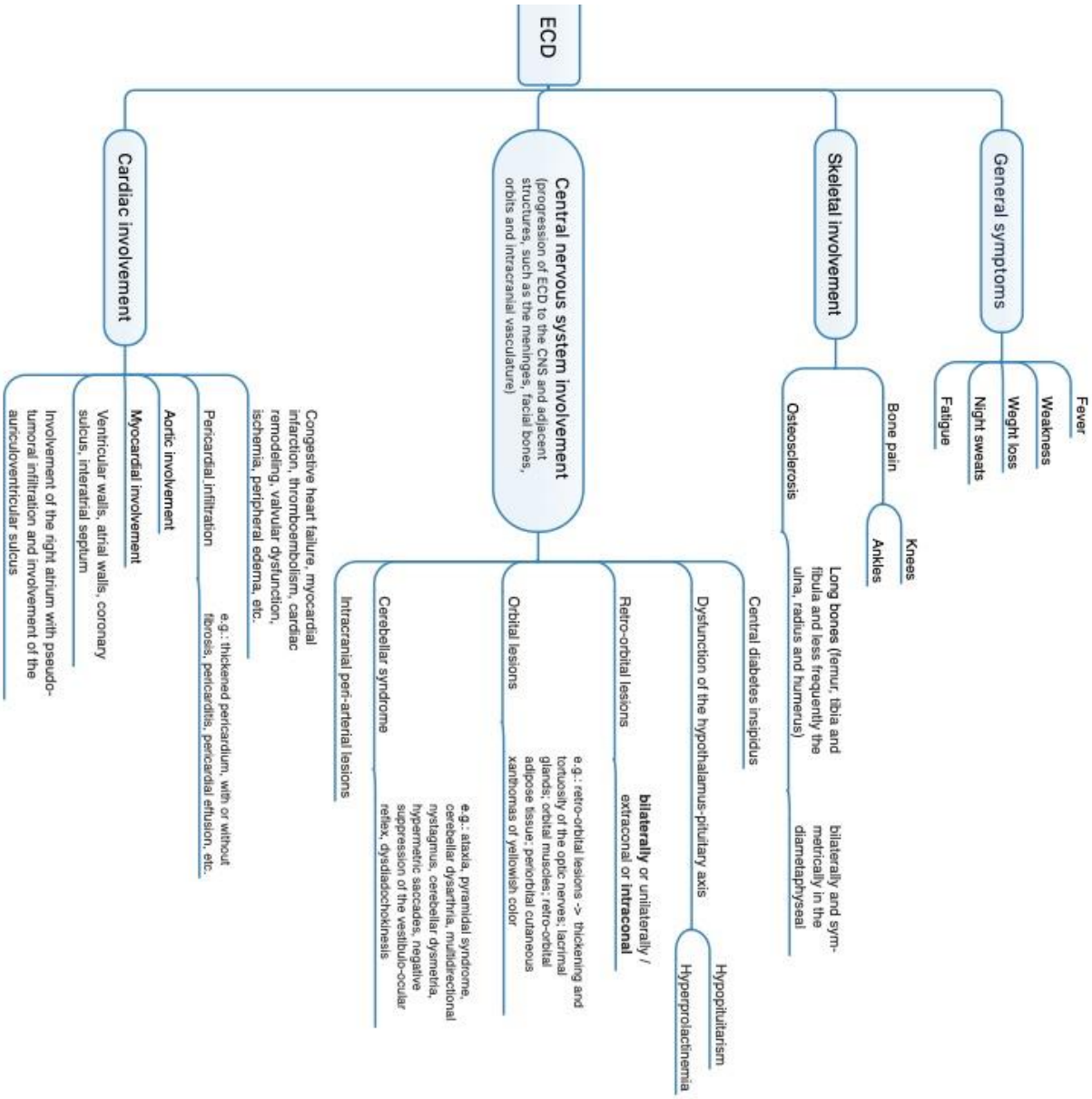


Fig. 10 – Overview ECD organ involvements and clinical manifestations, *part 2.*

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