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pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

DES de Pédiatrie

par

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DIFFICULTES DIAGNOSTIQUES ET THERAPEUTIQUES DE LA LYMPHANGIOMATOSE GENERALISEE AVEC ATTEINTE PULMONAIRE DIFFUSE CHEZ L'ENFANT : UNE SERIE DE CAS FRANÇAISE MULTICENTRIQUE

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SOMMAIRE

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TABLE DES ILLUSTRATIONS

INTRODUCTION

Les anomalies lymphatiques complexes sont des pathologies systémiques rares et agressives qui surviennent généralement dans l'enfance ou chez les adultes jeunes (1). Ces pathologies regroupent la lymphangiomatose généralisée (GLA), la maladie de Gorham-Stout (GSD) et la lymphangiomatose kaposiforme (KLA) considérée récemment par la Société internationale pour l'étude des anomalies vasculaires (ISSVA) comme un sous-type de GLA (2). Leur prévalence est difficile à estimer du fait de leur rareté et de leur sous-diagnostic, on estime que 10 à 30 nouveaux cas de GLA ou GSD naissent chaque année en Europe.

Celles-ci sont responsables d'une prolifération anormale de vaisseaux lymphatiques pouvant affecter de nombreux organes tels que la peau, les organes thoraciques ou abdominaux et les os. Les patients sont souvent diagnostiqués tardivement car les caractéristiques cliniques et radiologiques de ces pathologies sont variées et non spécifiques. L'existence de formes chevauchantes au sein même des anomalies lymphatiques complexes participe également à la confusion diagnostique (3,4). Malgré leurs similitudes, les distinguer reste indispensable puisque leur pronostic et leurs traitements sont distincts.

Le pronostic est sombre et davantage encore chez les patients atteints de GLA avec une atteinte pulmonaire prédominante (lymphangiomatose pulmonaire diffuse ou DPL) ou ceux atteints de KLA.

La prise en charge et le traitement de ces patients sont peu standardisés car basés sur de petites cohortes ou des séries de cas rapportées dans la littérature. La radiothérapie, la chirurgie, la chimiothérapie et l'interféron peuvent être efficace chez certains patients, sans avoir fait l'objet d'essais cliniques (5–8). Récemment, des études prospectives ont montré que les inhibiteurs de mTOR et de PIK3CA, déjà utilisés dans certaines malformations vasculaires, sont efficaces chez les patients atteints de GLA et de GSD (9,10). Par exemple, le sirolimus, un inhibiteur de mTOR est parfois envisagé en première intention après concertation multidisciplinaire. Néanmoins, une évaluation plus approfondie chez ces patients est justifiée, en particulier chez les patients atteints de DPL ou de KLA où peu de données sur l'efficacité de ce traitement sont disponibles (11).

La physiopathologie est partiellement comprise, des mutations somatiques activatrices dans les voies PIK3/AKT/mTOR et RAS/MAPK/MEK ont récemment été rapportées chez des patients atteints de GLA et KLA, justifiant ainsi l'utilisation de thérapies ciblées (12–14).

L’objectif principal de cette étude était de rapporter les cas français de GLA et GSD, en se focalisant dans un second temps sur les patients présentant une atteinte à prédominance respiratoire (KLA et DPL) traités par sirolimus.

ARTICLE

Diagnostic and therapeutic challenges of generalized lymphangiomatosis with diffuse pulmonary lymphangiomatosis in children: a French multicentre case series

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ABSTRACT

Introduction. Complex lymphatic anomalies are rare and aggressive systemic disorders of the lymphatic vascular system that occur mostly in children and young adults. Several entities coexist as generalized lymphangiomatosis (GLA), Gorham-Stout disease (GSD), and kaposiform lymphangiomatosis (KLA) with overlapping clinical and radiological characteristics. As a consequence, reaching a diagnosis can be quite a challenge. Due to their rareness, the current therapeutic options have remained limited. The recent discovery of somatic mutations in the *NRAS* and *PIK3CA* genes in GLA and KLA patients has, however, broadened the therapeutic options. Although some patients have recently been treated with mTOR or PIK3CA inhibitors, more evidence is needed to assess the benefit/harm ratio in these patients.

The aim of this study was to document the diagnostic and therapeutic difficulties through a series of cases of GLA/GSD, with a focus on patients with diffuse pulmonary lymphangiomatosis (DPL) and KLA.

Materials and Methods. A retrospective national study that included children under 18 years of age at diagnosis, with GLA, KLA, GSD, or DPL. Clinical, biological, radiological, and genetic data were collected.

Results. Twenty eligible cases were identified: Six cases of GSD and 14 cases of GLA. Among these, two cases of diffuse pulmonary lymphangiomatosis (DPL) and one case of KLA are described. Respiratory and skeletal symptoms were predominant. In these three patients, the effectiveness of sirolimus was variable. Moreover, the same somatic mutation in the *NRAS* gene (p.Q61R; c.182A>G) was identified by DNA sequencing of pleural tissue from these three patients.

Conclusion. This first French cohort of GLA and GSD highlights the difficulty with classifying these patients and their treatment, as well the variable efficacity of sirolimus. The recent description of new somatic mutations in the *NRAS* gene is reason to hope for therapeutic progress with this disease.

MOTS CLES

GENERALIZED LYMPHANGIOMATOSIS – GHORAM STOUT DISEASE – DIFFUSE PULMONARY LYMPHANGIOMATOSIS – KAPOSIFORM LYMPHANGIOMATOSIS – NRAS MUTATION – PIK3CA MUTATION – SIROLIMUS

ABBREVIATIONS

GLA	Generalized lymphangiomatosis
GSD	Gorham-Stout disease
KLA	Kaposiform lymphangiomatosis
DPL	Diffuse pulmonary lymphangiomatosis
ISSVA	International Society for the Study of Vascular Anomalies
MRI scan	Magnetic resonance imaging scan
DIC	Disseminated intravascular coagulopathy

Introduction

Complex lymphatic anomalies are rare and aggressive systemic disorders of the lymphatic vasculature, typically occurring in childhood or early adulthood (1). Generalized lymphangiomatosis (GLA), Gorham-Stout disease (GSD), and kaposiform lymphangiomatosis (KLA) are distinct pathologies in complex lymphatic anomalies.

These disorders can affect many organs such as skin, thoracic or abdominal organs, and bones, and they are often diagnosed late because the clinical and radiological features are varied and non-specific. Furthermore, complex lymphatic anomalies include overlapping patterns that contribute to diagnostic confusion (3,4). Despite their similarity, GLA and GSD are two different entities with a distinct prognostic outlook and treatment. The prognosis is worse in GLA patients with predominantly pulmonary involvement (diffuse pulmonary lymphangiomatosis or DPL) and with KLA, which is a new subtype of GLA according to the International Society for the Study of Vascular Anomalies (ISSVA) in 2018 (2) (Appendix 1).

Due to their rarity, the general knowledge regarding these diseases has only been obtained from small cohorts or case reports, and the patient care and treatment are not codified: radiotherapy, surgery, chemotherapy, and interferon have been tested in some patients, but clinical trials are lacking (5–8). Recently, prospective studies have determined that mTOR and PIK3CA inhibitors are effective in GLA and GSD patients (9,10). The mTOR inhibitor, sirolimus, is considered a first-line treatment in some cases, but further evaluation in these patients is warranted, particularly in patients with DPL or KLA (11). Somatic mutations in the PIK3/AKT/mTOR and RAS/MAPK/MEK pathways have recently been reported in a number of patients with GLA and KLA, thus justifying the use of these therapeutic entities in patients (12–14).

The aim of this project was to report French cases of GLA and GSD, focusing in a second phase on patients with predominantly respiratory disease (KLA and DPL) treated with sirolimus.

Materials and Methods

This descriptive study was approved by the Nantes University Hospital ethics committee.

Patient selection

Thirty-two centres affiliated with the French Society of Rheumatology and Paediatric Inflammatory Diseases, the French Society of Pediatric Dermatology, and the French network for rare vascular diseases were asked to compile information regarding paediatric cases with complex lymphatic malformations.

The inclusion criteria were a diagnosis of a complex lymphatic malformation such as GLA, GSD, KLA, or DPL as defined below, as well as being less than 18 years of age at the time of diagnosis.

Patients with polymalformative syndromes, combined vascular malformations such as capillary-lymphatic, lymphatic-venous, or capillary-lymphatic-arteriovenous malformations or with a history of radiation therapy or surgery that can cause secondary lymphatic malformations were excluded.

Definition of the study population

The definitions presented below are mainly based on the ISSVA classification and the overview by Ozeki et al. in 2019 (2,4) (Appendix 1 and Appendix 2).

The definition of GLA is divided into three subtypes: (i) DPL, a single-organ disorder characterized by diffuse and slow infiltration of the thoracic cavity by the lymphatic vessels causing pulmonary, mediastinal, and bone (mainly vertebrae and ribs) lesions ; (ii) multifocal GLA, characterized by the presence of individualized lymphangiomas in several organs[1], whereby the location determines the symptomatology of the patient (15,16) ; and (iii) KLA, classified as a subtype of GLA associated with more frequent haemorrhagic pleural and pericardial effusions and severe coagulation disorders. The histological hallmark of KLA is kaposiform, hemosiderotic, spindle-shaped lymphatic endothelial cells arranged in clusters (17).

Lastly, GSD is a skeletal disorder characterized by intraosseous proliferation of lymphatic vessels resulting in aggressive and progressive contiguous bone lysis with cortical involvement. The most common symptoms are pain and bone fractures. Rarely do extraosseous symptoms such as pleural effusions coexist (18).

Description of GLA and GSD cases

Data regarding the clinical, radiographic, and histopathological features, as well as the treatment were collected retrospectively.

The clinical signs included the general condition, respiratory (dyspnoea, cough, and chest pain), skeletal (pain and fractures), neurological (headache, intracranial hypertension), and abdominal (pain, transit disorder) symptoms.

Biological parameters such as inflammatory syndrome, haemostasis disorders, abnormal blood counts, and hypogammaglobulinemia were collected.

Chest X-rays, scans, or MRI scans of the chest, brain, or bones were available.

Therapeutic management was noted for all of the patients and detailed only for cases of KLA and DPL.

For GLA, a focus on DPL and KLA patients

For these patients, a detailed medical history and the clinical, biological, and radiological characteristics were reported.

The efficacy of sirolimus was evaluated by comparison of the clinical, biological, and radiological data before and after sirolimus administration.

Results

Selection of patients with GLA or GSD

Thirty-three potentially eligible cases were analysed. After having assessed them, 20 cases were selected and classified as outlined in the flowchart (Fig.1).

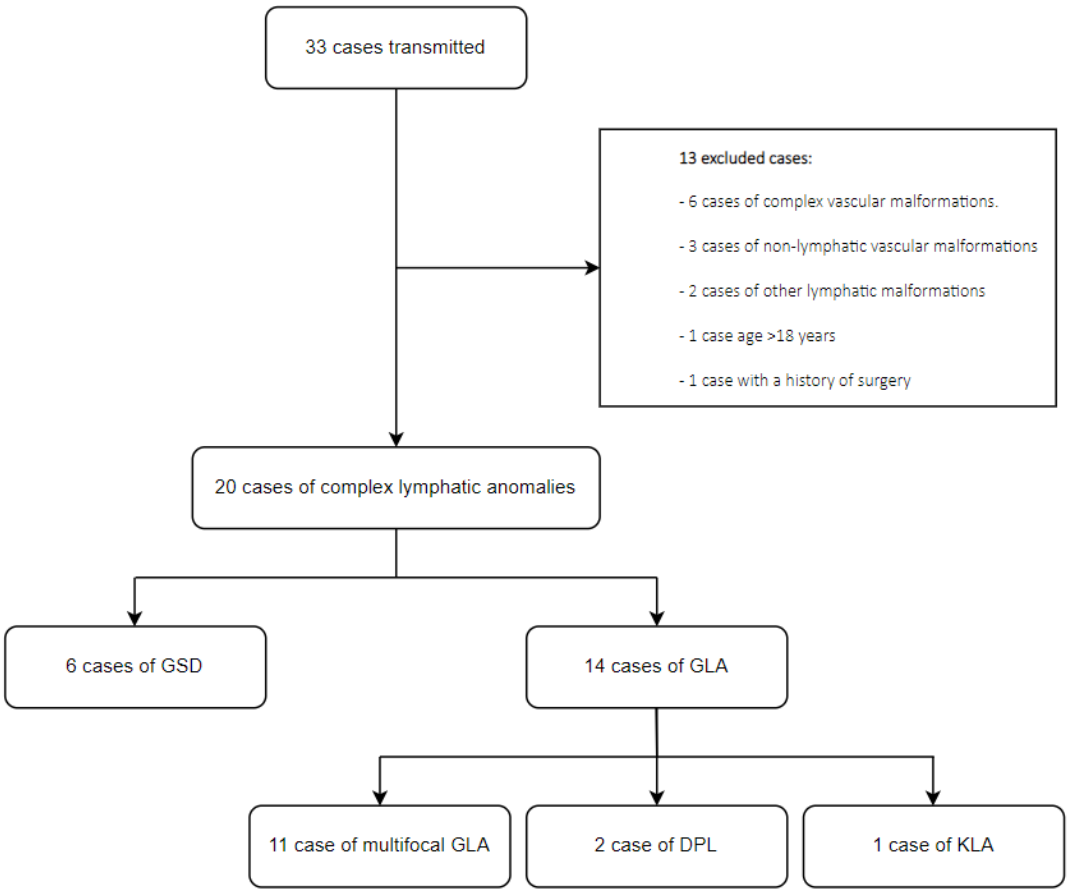

FIGURE 1. Flow chart

Description of the GLA and GSD cases

Their clinical, radiological, and biological features, as well as their therapeutic care are presented in Table 1. For the osseous injuries, the term “multiple locations” reflects the association of several lesions at different sites, whereas “contiguous location” pertains to injury in the adjacent bones. Cortical involvement was specified only when it was described in the imaging reports: cortical loss or not.

The median age of the cohort was 4 years. In only one case was the diagnosis made antenatally (patient 11), due to the presence of cervical soft tissue lesions on ultrasound. The sex ratio (M/F) was 2.3 [0 ; 17]

Eight patients were treated with sirolimus, involving monotherapy in one case. The treatment was surgical for 8 patients: pericardial drainage was performed in patient 2, exeresis of lymphangioma in patients 4, 5, 10, and 11, osteosynthesis in patients 15 and 17, while a middle ear exclusion and eustachian tube ligation were performed in patient 20.

TABLE 1. Clinical, radiological, and biological characteristics and treatment of the 20 cases of diffuse pulmonary lymphangiomatosis, Gorham-Stout disease, and multifocal lymphangiomatosis.

	Age at first symptoms (years)	Gender	Type/Subtype	Osseous injury	Bone locations	Respiratory injury	Chest imaging	Other injuries	Biology	Treatments	General surgery
Case 1	12	M	GLA/DPL	O/NCI/ML/NS	Cervical, thoracic, and lumbar spine, temporal bone	Dyspnoea, cough, pleural effusions	Lung and mediastinal infiltration	HSMG Intersplenopancreatic infiltrate AC type I malformation	DIC IS	SRL	
Case 2	13	F	GLA/DPL	None	-	Dyspnoea, pleural and pericardial effusion	Lung infiltration and mediastinal mass	HSMG Retrogastric and pancreatic infiltrates	DIC IS	VCR / CT / SRL	Yes
Case 3	2	M	GLA/KLA	None		Dyspnoea, cough	Lung and mediastinal infiltration	HMG AC type I malformation	DIC	CT / SRL / HNF	
Case 4	Childhood	M	GLA/Multifocal GLA	None		NA	Left chest wall involvement	LM of the two trapezoids and supraclavicular hollows	NA	SCT	Yes
Case 5	3	M	GLA/Multifocal GLA	O/ML/NS	Cervical spine, scapula. and pelvis	Dyspnoea, chest oppression	Hemithoracic and mediastinal macrocystic LMs	Subclavicular LM	NA	SCT	Yes
Case 6	3	M	GLA/Multifocal GLA	O/ML/S (limping)	Upper and lower limb	None	Normal	Micro and macrocystic retroperitoneal and inguinal LMs	NA	SCT	
Case 7	Neonatal	M	GLA/Multifocal GLA	NA	NA	NA	Latero-thoracic right LM	Axillary LM	NA		
Case 8	14	F	GLA/Multifocal GLA	O/S	Lumbar spine	None	Normal	Paravertebral LM with infiltration of the psoas	NA	NA	
Case 9	Neonatal	M	GLA/Multifocal GLA	No	-	None	None	Hepatic and splenic LM, LM with tendon infiltration, Lymphoedema	Blood count normal	CT / SRL	

	Age at first symptoms (years)	Gender	Type/Subtype	Osseous injury	Bone locations	Respiratory injury	Chest imaging	Other injuries	Biology	Treatments	General surgery
Case 10	12	F	GLA/Multifocal GLA	O/NCI/ML/S (pain)	Cervical, thoracic, and lumbar spine, iliac wing and sacrum	None	Normal	Left cervical LM	NA		Yes
Case 11	Antenatal	F	GLA/Multifocal GLA	O/NCI/ML/S (diffuse pain)	Thoracic and lumbar spine, humerus, scapula, ribs, femur	None	Normal	Splenic LM	Blood count normal No DIC	BP / SCT / SRL	Yes
Case 12	3	M	GLA/Multifocal GLA	O/NCI/NS	Iliac bones, sacrum, femur	Cough	None	Abdominal pain Lymphoedema (left thigh), Cutaneous papillomatosis	NA	None	
Case 13	14	M	GLA/Multifocal GLA	O/CI/ML/S (pain)	Cervical, thoracic and lumbar spine, iliac bone, right tibia, right and left femur	None	Normal	Splenic LM Musculo-skeletal LM (right upper limb)	Increased D-dimers Blood count normal	SRL / Elastic restraint	
Case 14	15	M	GLA/Multifocal GLA	O/NCI/ML/NS	Cervical spine, right and left femur, iliac wing	NA	Mediastinal mass	Splenic cysts	NA	NA	
Case 15	Neonatal	M	GSD	O/CL/S (fractures)	Right lower limb, right iliac wing	None	None	Lymphoedema and cutaneous lymphangiectasias	NA	BP / SRL	Yes
Case 16	2	F	GSD	O/S (PF)	Petrous bone	None	Normal	AC type I malformation	Blood count normal NIS	BP	
Case 17	6	M	GSD	O/ML/S (fractures)	Upper and lower limb, skull (orbit, mandible, mastoid, occipital bone), cervico-thoracolumbar spine, ribs	None	Cystic lymphangioma	Splenic cysts	NA		Yes

	Age at first symptoms (years)	Gender	Type/Subtype	Osseous injury	Bone locations	Respiratory injury	Chest imaging	Other injuries	Biology	Treatments	General surgery
Case 18	17	M	GSD	O/CL/S (bone pain)	Coxofemoral and iliac bone, ischium and pubis	None	None	None	NA	BP	
Case 19	13	F	GSD	O/CL/S (limping)	Femur and right ilium	None	Normal	None	NA	BP / IFN	
Case 20	4	M	GSD	O/CI/S (meningitis)	Petrous bone	None	Normal	IH AC type I malformation	Blood count normal No DIC	BP / IFN / SRL	Yes

Legend:

M	Male	IFN	Interferon
F	Female	SCT	Sclerotherapy
DPL	Diffuse pulmonary lymphangiomatosis		
GSD	Gorham-Stout disease		
GLA	Generalized lymphangiomatosis		
O	Osteolytic		
CI or NCI	Cortical involvement or no cortical involvement		
S or NS	Symptomatic or not symptomatic		
ML	Multiple location		
CL	Contiguous location		
NA	Not available		
HSMG	Hepatosplenomegaly		
HMG	Hepatomegaly		
IH	Intracranial hypertension		
AC type I malformation	Arnold Chiari type I malformation		
LM	Lymphatic malformation		
DIC	Disseminated intravascular coagulopathy		
SRL	Sirolimus		
VCR	Vincristine		
CT	Corticosteroids		
BP	Bisphosphonates		

Description of the DPL cases

The clinical, biological, and radiological features, as well as the therapeutic management for these three patients are compared in Tables 2 and 3, and the medical history is detailed below.

TABLE 2. Clinical, radiological, biological and histological characteristics of each case of diffuse pulmonary lymphangiomatosis

Characteristics	Case 1	Case 2	Case 3
Sexe	Boy	Girl	Boy
Age of first symptoms	13 years old	14 years old	2 years old
Past history	asthma, intracranial hypertension, bradykinic oedema	dental agenesis	asthma, facial paralysis, recurrent infections
Initial diagnosis	Bradykinic oedema crisis	Mediastinal lymphoma	Pneumonia
Diagnostic delay	1 year	5 months	2 years
Clinical characteristics:			
Alteration of the general condition	Y[1]	Y	Y
Respiratory symptoms			
Dyspnea	Y	Y	Y
Cough	N[2]	N	Y
Thoracic pain	N	Y	N
Digestive symptoms			
Peritonitis	Y	N	N
Abdominal pain	Y	Y	N
Neurological symptoms			
Headaches	Y	N	Y
Intracranial hypertension	N	N	Y
Arnold Chiari Malformation	Y, type I	N	Y, type I
Osseous symptoms			
Osseous pain	N	N	N
Fractures	N	N	N
Radiological characteristics:			
Chest			
Pleural effusion	Y	Y	N
Pericardial effusion	Y	Y	N
Peri-bronchovascular infiltration	Y	Y	Y
Mediastinal mass	Y	Y	Y
Mediastinal infiltration	Y	Y	Y
Abdomen			
Hepatomegaly	Y	Y	N
Splenomegaly	Y	N	Y

[1] Yes
[2] No

TABLE 3. Therapeutic management and efficacy of sirolimus in the two treated cases out of three reported cases of diffuse thoracic lymphangiomatosis

Therapeutic management	Case 1	Case 2	Case 3
Previous treatment :			
Medical treatment	corticosteroids, antibiotics, B2 mimetics	N	Antibiotics, IgIV
Chirurgical treatment	N[2]	pleural and pericardial drainage	N
Treatment by Sirolimus	Y[1]	Y	Y
Delay between diagnostic and sirolimus start time	1 month	10 days	
Associated treatments	N	vincristine / corticosteroids	Corticosteroids/anticoagulants
Hindsight time	30 months	18 months	6 months and stop
Efficacy of sirolimus treatment			
Clinical Efficacy :	Y	Y	
Dyspnea improvement	Y	Y	
Improvement of the general condition	Y	Y	
Improving quality of life	Y	Y	
Radiological Efficacy :	N	Y	
Pulmonary infiltration	stabilization	stabilization	
Pleural effusion	stabilization	decrease	
Pericardial effusion	increase	decrease	
Mediastinal infiltration	stabilization	decrease	
Bones lesions	stabilization	/	
Biological Efficacy :	Y	Y	N
Intravascular coagulation	improvement	improvement	Severe intravascular coagulation
Inflammatory syndrome	disappearance	disappearance	

Case 1

A 12-year-old boy was hospitalized for aseptic peritonitis. He had a history of iterative lumbar punctures for episodes of intracranial hypertension at 4 years of age. Cerebral magnetic resonance imaging revealed a type I Arnold Chiari malformation. At 5 years of age, a diagnosis of bradykinin-mediated angioedema was established in the presence of recurrent urticarial symptoms. At 10 years of age, he developed germ-free meningitis. A paracentesis (suspicion of serous otitis media) found a right petrous meningoencephalocele revealing a meningeal breach. A CT scan of the skull base revealed lytic lesions of the right petrosal bone.

When he developed his aseptic peritonitis, he was admitted to the intensive care unit after the surgery because he had developed acute respiratory failure due to a profuse right pleural effusion. This episode was initially considered to be a bradykinin-mediated angioedema crisis

associated with *Streptococcal A pneumoniae*. Treatment with tranexamic acid and antibiotics was partially effective. The clinical change after 8 months was marked by an alteration in his general condition and frequent hospitalizations for pleuropneumonias or asthmatic exacerbations. Sequential corticosteroid therapies were ineffective.

The extensive investigations for autoimmune, metabolic, and malignant diseases were negative. The laboratory examination revealed a fluctuating hypereosinophilia of up to 10 430/mm^3 without aetiology (parasitological, genetic, and autoimmune tests were negative). Abnormalities of haemostasis were present: prothrombin time 56%, factor values were low: factor II value of 69%, factor V value of 51%, factor VII value of 46%, and factor X value of 62%, and the fibrinogen concentration was 1.9 g/L. Hepatic lesion was suspected, but a D-dimer level of 8 074 ng/ml was secondarily suggestive of disseminated intravascular coagulation. Chest computed tomography revealed peribronchovascular and mediastinal infiltration, a bilateral pleural effusion, as well as retroperitoneal infiltration. The patient also had asymptomatic bone lesions of the cervical, thoracic, and sacral vertebrae (Fig.2).

At the age of 14, a diagnosis of diffuse pulmonary lymphangiomatosis was confirmed after several pleural and lung biopsies. Genetic analyses identified a somatic activating *NRAS* mutation (p.Q61R; c.182A>G) in the lesional tissue.

Treatment with sirolimus (residual level between 4 and 7 ng/ml), started at the time of diagnosis, resulted in clinical and biological improvement, partial improvement of the pulmonary radiological abnormalities, and stabilisation without improvement of the vertebral bone lesions (Table 3).

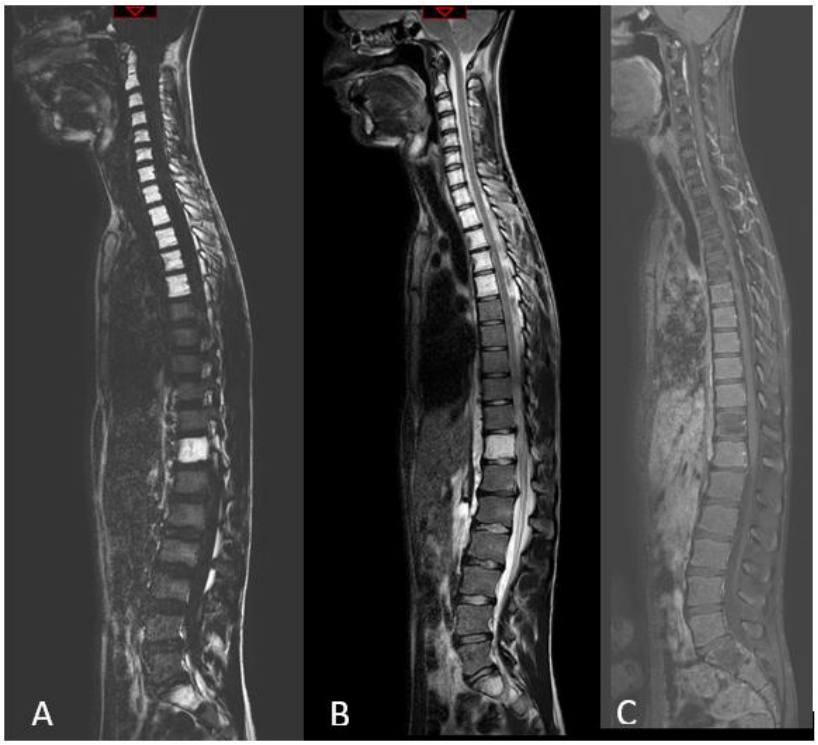

FIGURE 2. Magnetic resonance imaging showing signal abnormalities of the cervicothoracic vertebrae from C1 to T5 of T11 and S1 of case 1.
Vertebral infiltrates in hypersignal T1-T2 (A et B) which disappears on the fat saturation sequences (C) probably related to the fat content of the infiltration.

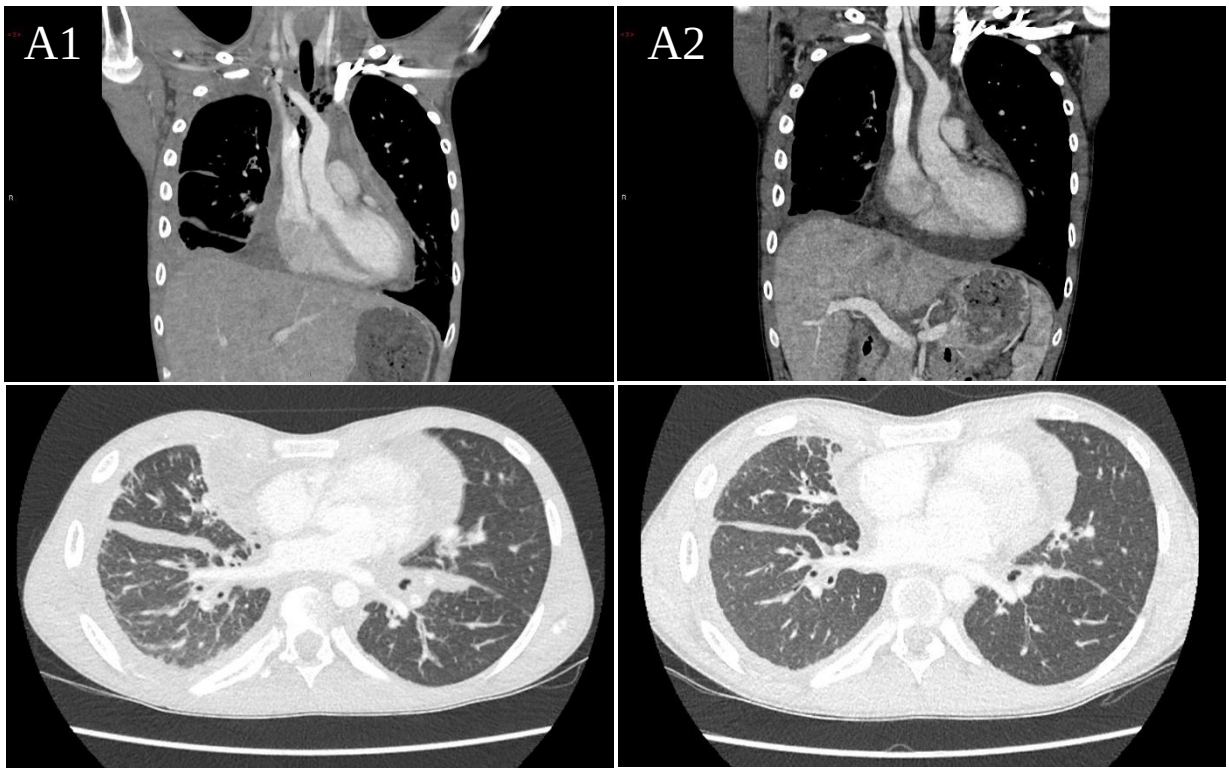

FIGURE 3. Thoracic TDM of patient 1 before (A1 B1) and after 4 months of sirolimus treatment (A2 B2)
A: worsening of the pericardial effusion or infiltration, decrease of the mediastinal infiltration.
B: decrease in peribronchovascular and septal thickening, persistence of right pleural effusion.

Case 2

A 14-year-old girl who for several months exhibited alteration of her general condition, and rapid weight loss associated with dyspnoea and abdominal pain. She had an unremarkable prior medical history.

The chest imaging revealed abundant bilateral pleural effusions associated with a mediastinal mass. In this context, a malignant pathology such as a lymphoma was suspected. Laboratory examinations revealed an elevated LDH value of 606 U/L, a normal blood count, and moderate haemostasis disorders with a prothrombin time of 58%, factor V value of 59%, a fibrinogen concentration of 2.2 g/L, and a D-dimer concentration of 7 318 ng/ml (normal < 500 ng/ml).

After drainage of the pleural effusions, the patient developed massive loss of chyle via chest drains that caused hypovolemic shock and severe respiratory distress. Biopsy of the mediastinal mass was again followed by a clinical and hemodynamic decline related to a cardiac tamponade. An emergency surgical intervention was performed.

A chest CT and pathological examination of pleural fragments confirmed the diagnosis of diffuse pulmonary lymphangiomatosis. Genetic analyses identified the same somatic activating *NRAS* mutation (p.Q61R; c.182A>G) in the lesional tissue.

Due to the severity of the clinical situation, treatment with vincristine (2 doses one week apart) was introduced in combination with high-dose corticosteroid therapy (2 mg/kg/day) and sirolimus at 2.5 mg/day. The patient was provided a diet enriched in medium-chain triglycerides.

Rapid improvement in the patient's condition was observed, with a decrease in pleural effusions. One week after the beginning of the treatment, sirolimus was continued as a monotherapy, with a residual serum level target of 4-7 ng/ml. After 7 months of treatment, overall efficacy (clinical, biological, and radiological) was observed (Table 3). The coagulation disorders regressed, with a normal prothrombin time of 72%, a fibrinogen concentration of 2.7 g/L, and a D-dimer concentration of 570 ng/ml. The initial thoracic scan and the scan performed 5 months after the start of treatment are shown side-by-side for comparison (Fig.3).

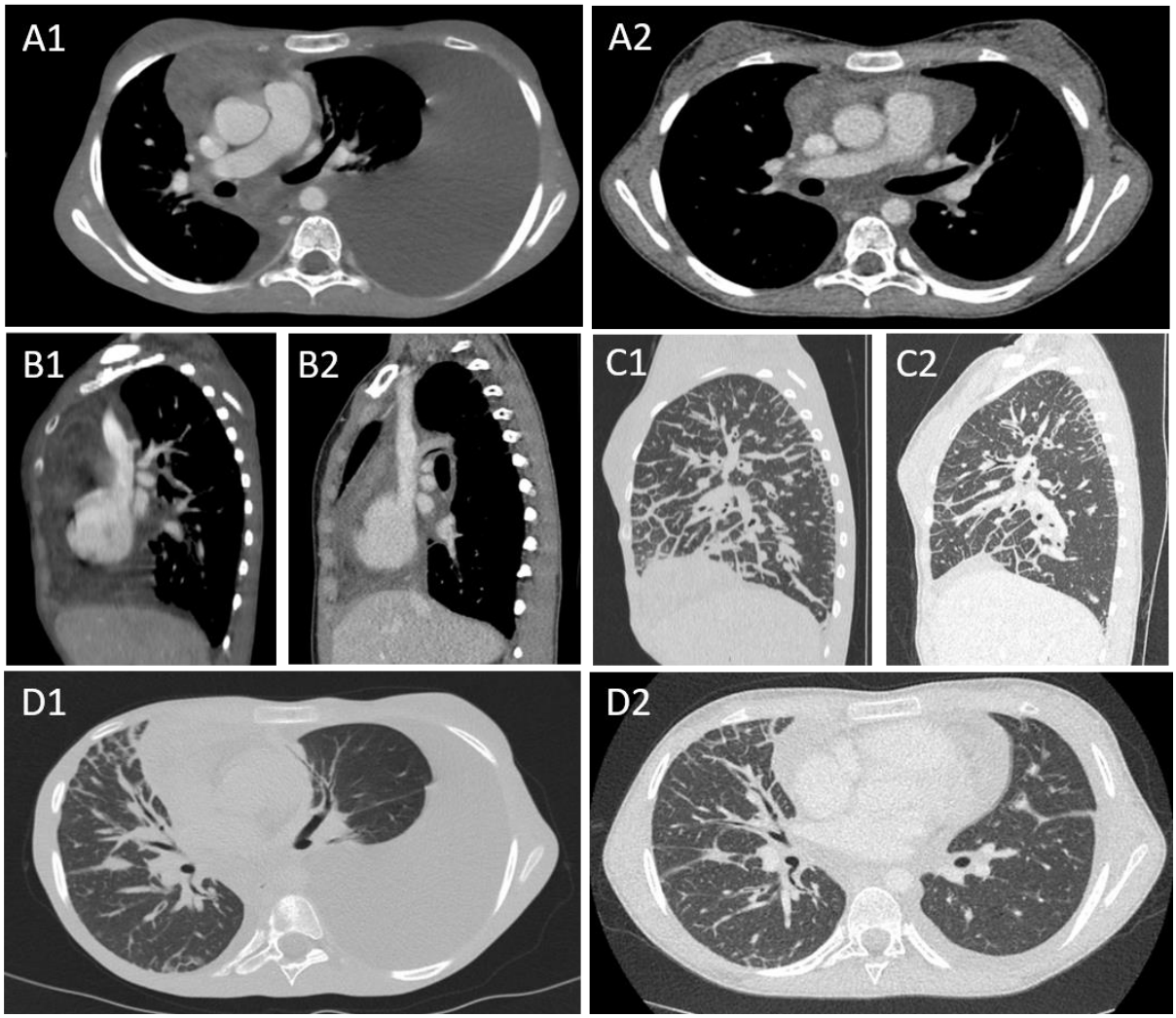

FIGURE 3. Thoracic TDM of patient 2 before (A1 B1 C1 D1) and after five month of treatment by sirolimus (A2 B2 C2 D2)
A : decrease of mediastinal infiltration and volume of pleural effusion.
B : decrease of mediastinal infiltration
C et D : decrease peribronchovascular infiltration and septal thickening.

Case 3

The third case was a boy. At two years of age, he exhibited a respiratory disorder with dyspnoea and cough associated with an alteration in his general condition.

His past medical history revealed multiple infections: otorhinolaryngology infections, pneumococcal meningitis, and pneumococcal pneumonia.

These repeated infections were suggestive of an immune deficiency. He was treated, therefore, with intravenous immunoglobulin at one year of age. Extensive investigations revealed a reduced humoral response.

This new respiratory episode with an altered general condition first led to a diagnosis of infectious pneumopathy. After one year of treatment, the persistence of symptoms and the right pulmonary opacities on the chest X-ray called for additional examinations.

A chest CT revealed bilateral parenchymal infiltration with septal thickening and mediastinal infiltration. A review of the clinical and radiological records and the lack of improvement despite appropriate antibiotic and immunoglobulin therapies led to the diagnosis of diffuse pulmonary lymphangiomatosis at four years of age.

Genetic analyses identified the same somatic activating *NRAS* mutation (p.Q61R; c.182A>G) in the lesional tissue. The diagnosis of KLA was made on the basis of all of the clinical, biological, and genetic criteria.

At the same time, he exhibited disabling headaches and signs of intracranial hypertension. A craniostenosis was discovered by magnetic resonance imaging, and a surgical intervention was performed. A type I Arnold Chiari malformation was visible on the brain images.

Treatment with sirolimus was started, combined with anticoagulants and corticosteroids six months later at the time of a severe DIC attack. After this complication, the administration of sirolimus was stopped.

Discussion

In this retrospective case series of 20 children with complex lymphatic anomalies, we highlight the difficulties with making a diagnosis. Focusing on KLA and DPL, we report the same mutation *NRAS* (p.Q61R; c.182A>G) in three patients and a variable efficacy of sirolimus.

Complex lymphatic anomalies are difficult to classify. Firstly, the definitions are sometimes unclear, and the terms used to refer to the diseases often differ depending on the study. For example, in this cohort, 11 patients were excluded due to misdiagnosis.

The first challenge was then to segregate the 20 children into GLA (including DPL, multifocal GLA, and KLA) versus GSD through a combination of clinical, radiological, and biological features (4). As previously described, bone lesions were predominant in these patients (6/6 patients with GSD and 9/14 patients with GLA) and they are useful for distinguishing between GLA versus GSD (3,19).

In our study, compared to the GLA patients, the patients with GSD more frequently had cranial lesions (3/6 patients), with the affected bones most often being contiguous (3/6 patients), and all of the patients exhibited predominant bone signs with fractures, pain, and

limping (3,4). The cortical damage commonly described in GSD cohorts could not be assessed due to missing data. Our GLA patients more often suffered from staged vertebral damage (7/9 patients) (20). The osteolytic lesions affected numerous non-contiguous bone locations (7/9 patients), without resorption and cortical loss, and all of the patients exhibited extraosseous involvement (14/14) (3,4,19). As bone damage is only symptomatic in 5 out of 9 patients with GLA, it would be interesting to systematically provide a radiological evaluation for GLA patients as proposed by Iacobas and al. (21). A certain degree of overlapping shapes, such as in patient 6 (classified as GSD although his additional bone injuries are also compatible with GLA), complicates the diagnosis, which dictates the treatment to be provided. As was the case for 5 out of 6 patients in our GSD cohort, GSD patients are treated mainly with bisphosphonates based on the partially elucidated physiopathology, which involves proliferation of lymphatic vessels, and a significant degree of osteoclast-mediated bone remodelling occurs in the affected bone structures (4,22).

Interestingly, in this study, Arnold Chiari type I malformation was found in one patient with DPL, one patient with KLA, and two patients with GSD, and was associated with lesion of the petrous temporal bone in three patients. Although this malformation is not specific to complex lymphatic anomalies due to its high frequency in the general population (estimated to occur in 1%) (23,24), it has nevertheless been reported in five patients with GSD and one with GLA with cranial bone damage (25,26).

Here, we chose to distinguish three entities within GLA: multifocal GLA, DPL, and KLA, because their treatment and prognosis are different. Chest involvement in these patients is common and can be confusing. Four patients with multifocal GLA had thoracic involvement, and imaging revealed cystic lesions in the lungs and the mediastinum. These radiological features in patients were reported by Laverdière et al. as “diffuse systemic lymphangiomatosis”, which contributes to the confusion of these pathologies (6). The presence of lymphangiomas in different organs (splenic or hepatic cysts or macrocystic lymphatic malformations) allows diagnosis of multifocal GLA, differentiating it from isolated lymphangioma (27). As shown previously in the literature, in this study, thoracic imaging of DPL patients and KLA patients was often characterized by diffuse interlobular septal thickening, pleural effusion, and mediastinal soft tissue infiltration (28,29). The pulmonary damage in patients 1 and 2 is characteristic of DPL, but the presence of retroperitoneal infiltrates has not been reported in the literature for DPL, although it is present in patients with KLA (30).

DPL and KLA are characterized by a predominant respiratory disorder with infiltration of the pulmonary parenchyma associated with pleural and pericardial effusions. The damage appears to be more severe in patients with KLA, and the presence of spindle cells in the tissue is specific (17,31). In our study, the patients with DPL had similar clinical characteristics as the patients with KLA. Indeed, they exhibited a high degree of respiratory and retroperitoneal involvement, haemorrhagic effusion, and DIC that may be indicative of a kaposiform lymphangiomatosis, but the histological analysis did not confirm this hypothesis. Due to the distribution of the spindle cells into sparse and poorly marginated clusters, the absence of spindle cells in the anatomopathological analysis in these two patients could be explained by a site-specific effect of the biopsy (32). Since these pathologies are difficult to distinguish clinically and sometimes histologically, the study of KLA biomarkers such as angiogenic cytokines (VEGF3 and angiopoietin 2) could improve their distinction (33).

Genetic advances could also help classify and diagnose these pathologies. In our cohort, a somatic gain-of-function mutation in the *NRAS* gene (p.Q61R; c.182A>G) was found in pleural biopsies in two patients with DPL and one with KLA. This mutation in the *NRAS* gene has already been reported in the literature in 10 patients with KLA and in one with DPL (13,14). In an article by Manevitz-Mendelson et al., the patient with an NRAS mutation had a diagnosis of DPL but histological analysis revealed the presence of kaposiform cells. Rodriguez-Laguna et al. also identified four distinct *PIK3CA* variants in five out of nine patients with multifocal GLA (34). PIK3CA mutations are also found in patients with lymphatic malformations as part of a syndromic form (CLOVES syndrome, Klippel-Trenaunay syndrome) and in a number of isolated lymphatic malformations (12). The patients with multifocal GLA in this study have not been studied genetically. The PIK3/AKT/mTOR and RAS/MAPK/MEK pathways, already prominent in oncology, are also involved in lymphangiogenesis: their activation induces lymphatic cell proliferation (34,35) (Appendix 3). Finally, the existence of a geno-phenotypic entity: LDT/KLA with *NRAS* mutation and multifocal GLA with *PIK3CA* mutation is a consideration and would help in their classification as well as in their therapeutic management. A systematic search for mutations in these patients should nevertheless be given due consideration, as it can cause post-biopsy complications, as was the case for patient 2 (36).

Until recently, treatment strategies for these patients were not codified, and they were only reported in isolated cases. Treatment with the mTOR inhibitor sirolimus appears to be effective at stabilizing or reducing disease symptoms in patients with GLA or GSD (34). Only a small number of DPL patients treated with sirolimus have been reported in the literature

(11,37). For our patients with DPL who were treated with sirolimus, patient 2 had a clinical, biological, and radiological response and patient 1 had a clinical and biological response only. In the study by Ricci et al. regarding the efficacy of sirolimus in eighteen patients with GLA or GSD, only 28% had radiological improvement of the lung lesions (38). As the time of action of sirolimus is approximately 10 weeks, the rapid improvement of clinical symptoms and radiological lesions in patient 2 was presumably due to the combination of corticosteroids and vincristine prescribed in case of severe presentations (39,40). In non-responder patients or partial responders to sirolimus, the treatment options have been poorly described. Venot et al. in 2018 reported the efficacy of the PIK3CA inhibitor alpelisib in a cohort of 19 patients with PIK3CA-related overgrowth syndrome, although to our knowledge it has never been used in cases of GLA or DPL (41). In patients with activating somatic mutations of *NRAS*, inhibitors of the RAS/MAPK/MEK pathway could have therapeutic potential, although evidence is lacking (35,42). Interestingly, the MAPK inhibitor trametinib appears to be effective on lymphatic malformations in patients with pathologies with mutations in the RAS pathway (43). There are currently no specific inhibitors of NRAS.

The major limitation of this study is its retrospective design. In addition, the cohort is probably non-exhaustive: collecting data was difficult due to the large panel of specialists involved in the follow-up of these patients, which depended on the location of the lesions (e.g., haematologists, pneumologists, gastroenterologists, internists, radiologists, etc.). The creation of a registry could facilitate future studies. Moreover, a degree of misclassification could have occurred in this study due to the patients' heterogeneous symptoms, and there are in fact overlapping forms, as described by Ozeki et al. in 2019 (4). The diagnosis and the distinction between these pathologies are based on clinical and radiological criteria, and histological analysis was not always available in this cohort. This classification could be improved by genetic analysis. In this study, we did not consider details regarding the follow-up of these patients, which can also be complicated due to poorly codified practice. For this purpose, in 2019, a committee of multidisciplinary experts established guidelines for the diagnosis and evaluation of complex lymphatic anomalies (21).

In conclusion, the data for this cohort confirm that the diagnosis of complex lymphatic anomalies is difficult and often delayed. A register could be provided to various societies to improve the classification and management of these disorders. Treatment with sirolimus appears to be partially effective in some patients with DPL, although this needs to be confirmed in larger cohorts. Through the discovery of somatic mutations, targeted therapies will probably provide new perspectives in non-responder patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

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CONCLUSION

Cette étude rétrospective multicentrique rapporte la première cohorte française d'enfants atteints d'anomalies lymphatiques complexes composée de six patients atteints de GSD et de quatorze patients atteints de GLA. Elle met en évidence, au vu du nombre élevé de cas exclus, les difficultés diagnostiques que peuvent rencontrer les praticiens face à ces pathologies.

Les atteintes osseuses et pulmonaires sont les plus fréquentes et permettent par leurs différences de distinguer les patients atteints de GLA et de GSD pour l'atteinte osseuse et les patients atteints de GLA multifocale, de KLA ou de DPL pour l'atteinte pulmonaire (3,4).

Dans un deuxième temps, nous avons choisi de nous focaliser sur les deux patients atteints de DPL et le patient atteint de KLA. La frontière entre ces deux pathologies est mince, en effet la description de l'atteinte clinique et radiologique pulmonaire de ces trois cas est peu discriminante, seule l'histologie permettrait de les distinguer par la présence de cellules lymphatiques fusiformes (17). De manière intéressante et déjà constatée dans la littérature chez 10 patients atteints de KLA et un patient atteint de DPL, une mutation somatique gain de fonction dans le gène *NRAS* (c.182G>A) a été retrouvée au sein des cellules du tissu lésionnel chez ces trois patients (13,14). D'autres mutations somatiques ont été rapportées, par exemple au sein du gène *PIK3CA* chez 5 patients atteints de GLA (34). Le rôle de ces mutations somatiques dans la physiopathologie de ces maladies est plausible car l'activation des voies PIK3/AKT/mTOR et RAS/MAPK/MEK est responsable entre-autre d'une prolifération des vaisseaux lymphatiques (44,45).

La découverte de mutations somatiques activatrices chez ces patients permet d'espérer de nouvelles perspectives thérapeutiques. Dans la littérature, des études prospectives réalisées chez des patients atteints de GLA ou de GSD ont montré une efficacité du sirolimus, un inhibiteur mTOR (9,10). Dans cette étude, deux patients atteints de DPL et un patient atteint de KLA ont été traités par sirolimus avec une efficacité variable. Chez les patients insuffisamment améliorés par le sirolimus, les options thérapeutiques ont été peu décrites. Venot et al. en 2018 ont rapporté l'efficacité de l'alpelisib, un inhibiteur de PIK3CA, dans une cohorte de 19 patients atteints de syndromes liés à une mutation PIK3CA (CLOVES syndrome…), ce traitement n'a à notre connaissance jamais été utilisé en cas de GLA ou de DPL (41). Chez les patients présentant des mutations somatiques activatrices de *NRAS*, les inhibiteurs de la voie RAS/MAPK/MEK pourraient avoir un potentiel thérapeutique. Le trametinib, par exemple, un inhibiteur de MAPK, semble être efficace sur les malformations lymphatiques chez des patients atteint de pathologies avec mutation dans la voie RAS (43).

En conclusion, les données de cette cohorte confirment que le diagnostic des anomalies lymphatiques complexes est difficile et souvent retardé. La création d'un registre afin de colliger les cas d'anomalies lymphatiques complexes pourrait améliorer la classification et la prise en charge de ces pathologies. L'efficacité du sirolimus est variable selon les patients mais on ne peut conclure dans cette étude du fait d'effectifs très réduits. Grâce à la découverte de mutations somatiques dans les voies PIK3/AKT/mTOR et RAS/MAPK/MEK, les thérapies ciblées offriront probablement de nouvelles perspectives chez les patients non répondeurs.

APPENDIX

APPENDIX 1. 2018 ISSVA classification of lymphatic malformations

Simple vascular malformations IIa

Lymphatic malformations (LM)

- Common (cystic) LM
  - Macrocystic LM
  - Microcystic LM
  - Mixed cystic LM
- Generalized lymphatic anomaly (GLA)
  - Kaposiform lymphangiomatosis
- LM in Gorham-Stout disease
- Channel type LM
- « Acquired » progressive lymphatic anomaly
- Primary lymphedema
- Others

APPENDIX 2. Figure representing the different types of lymphatic complex anomalies based on the article by Oseki et al in 2019.

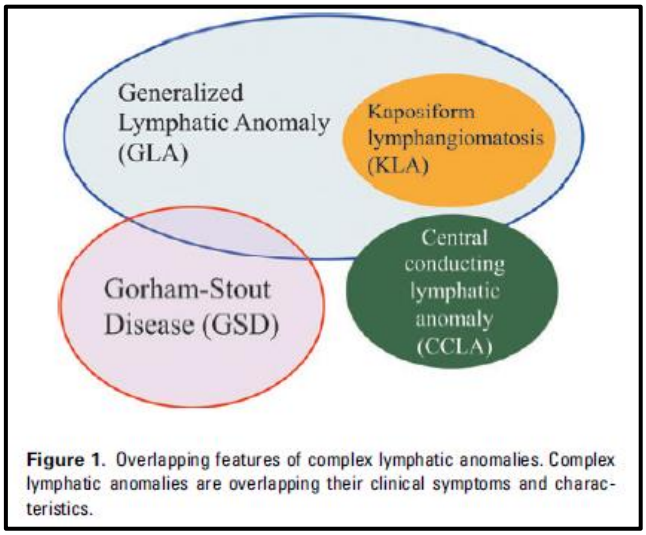
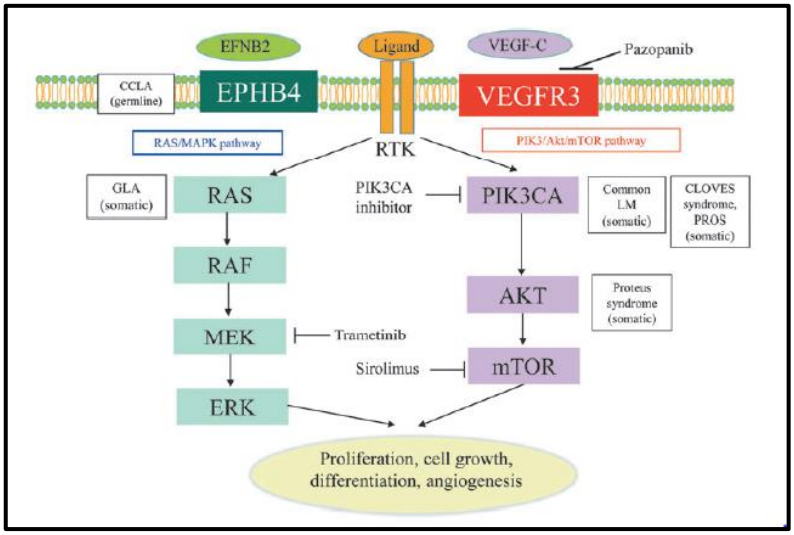


Figure 1. Overlapping features of complex lymphatic anomalies. Complex lymphatic anomalies are overlapping their clinical symptoms and characteristics.

APPENDIX 3. Involvement of PIK3CA/AKT/mTOR and RAS/MEK/MAPK pathways in angiogenesis based on the article by Oseki et al, 2019.



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Titre de Thèse : DIFFICULTES DIAGNOSTIQUES ET THERAPEUTIQUES DE LA LYMPHANGIOMATOSE GENERALISEE AVEC ATTEINTE PULMONAIRE DIFFUSE CHEZ L'ENFANT : UNE SERIE DE CAS FRANÇAISE MULTICENTRIQUE

RESUME

Les anomalies complexes lymphatiques regroupant la lymphangiomatose généralisée (GLA), la maladie de Gorham-Stout (GSD) et la lymphangiomatose kaposiforme (KLA) sont des maladies rares et agressives. Le diagnostic en est le plus souvent difficile du fait de leur rareté mais aussi de l'existence de formes chevauchantes entre ces entités. La découverte récente de mutations somatiques dans les gènes *NRAS* et *PIK3CA* chez ces patients permet de proposer de nouvelles thérapeutiques tels que les inhibiteurs de mTOR ou de PIK3CA.

L'objectif était de rapporter les cas français d'anomalies complexes lymphatiques afin de souligner les difficultés diagnostiques et thérapeutiques de ces pathologies puis de se focaliser dans un second temps sur les cas de lymphangiomatose diffuse pulmonaire (DPL) ou KLA.

On rapporte six patients atteints de GSD et 14 patients de GLA dont deux cas de DPL et un cas de KLA. Chez ces trois patients, l'efficacité du sirolimus était variable. La même mutation somatique dans le gène *NRAS* (p.Q61R; c.182A>G) a été identifiée par le séquençage de l'ADN du tissu lésionnel de ces trois patients.

Cette première cohorte française de GLA et GSD souligne la difficulté de classification de ces patients ainsi que de leur prise en charge thérapeutique. La description récente de nouvelles mutations somatiques des gènes *NRAS* et *PIK3CA* permet d'envisager des progrès thérapeutiques dans ces pathologies.

MOTS-CLES

LYMPHANGIOMATOSE GENERALISEE – MALADIE DE GORHAM-STOUT – LYMPHANGIOMATOSE DIFFUSE PULMONAIRE – LYMPHANGIOMATOSE KAPOSIFORME – MUTATION NRAS – MUTATION PIK3CA - SIROLIMUS