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Analysis of gene PIK3CA mutation in patients with lymphatic malformations

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Lymphatic malformations are type of vascular malformations, which are caused by disorders in development of lymphatic system. Lesions are benign and have tendency to progress during child development. Lesions may cause deformations of the body, disorders in physical development of the patient, disorders in physiological functions, or can even be life – threatening.

Lymphatic malformations are often painful and may impair everyday activities.

Main objectives of the research

Analysis of the occurrence and type of gene PIK3CA mutation in patients with lymphatic malformations.

Assessment of the occurrence of gene mutation, as a potential factor for targeted therapy.

Methodology

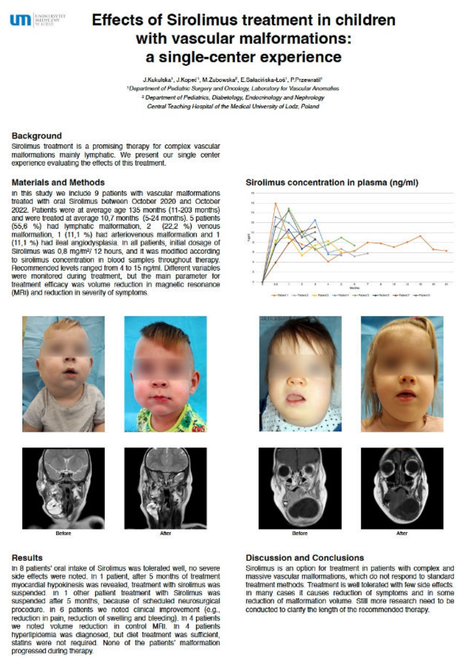
1. Election of the patients who meet inclusion criteria;
2. Obtaining sections from the paraffin embedded tissue blocks;
3. ddPCR analysis in search for the gene PIK3CA mutation (in cooperation with CORE LAB);
4. Analysis of the results.

Inclusion criteria

- Age <18 y.o. at the moment of diagnosis
- Patients with isolated lymphatic malformations
- Patient with CLOVES syndrome
- Patients with Klippel-Trenaunay syndrome

Other activities

- Oral presentation „Zastosowanie rekonstrukcji 3D w zabiegach operacyjnych guzów przestrzeni zaotrzewnowej u dzieci”, *XIX Meeting Problems in Pediatric Surgery* in Warsaw, December 2022
- Poster session ‘Effects of Sirolimus treatment in children with vascular malformations: a single-center experience’, *Conference of Vascular Anomalies* in Brussel, February 2023
- Poster session “Ropień wątroby o nieznanej etiologii-opis przypadku”, *XVIII Meeting of Polish Pediatric Surgeons Association* in Poznan, September 2022
- International internship in Hospital Universitario La Paz in Madrid, 5-30 June 2023



Effects of Sirolimus treatment in children with vascular malformations: a single-center experience

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Background
Sirolimus treatment is a promising therapy for complex vascular malformations mainly lymphatic. We present our single center experience evaluating the effects of this treatment.

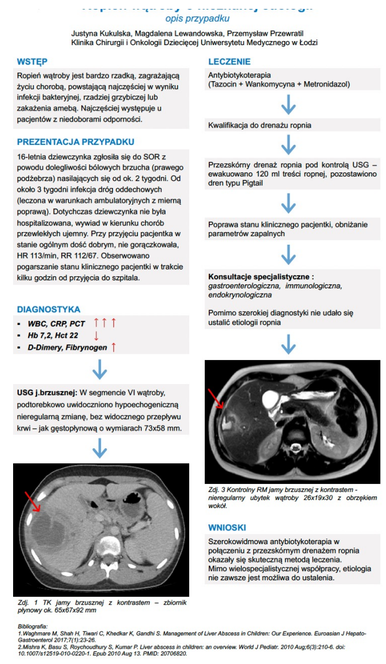
Materials and Methods
In this study we include 9 patients with vascular malformations treated with oral Sirolimus between October 2020 and October 2022. Patients were at average age 135 months (11-203 months) and were treated at average 10,7 months (5-24 months). 5 patients (55,6 %) had lymphatic malformation, 2 (22,2 %) venous malformation, 1 (11,1 %) had arteriovenous malformation and 1 (11,1 %) had ileal angiodysplasia. In all patients, initial dosage of Sirolimus was 0,8 mg/m² 12 hours, and it was modified according to sirolimus concentration in blood samples throughout therapy. Recommended levels ranged from 4 to 15 ng/ml. Different variables were monitored during treatment, but the main parameter for treatment efficacy was volume reduction in magnetic resonance (MRI) and reduction in severity of symptoms.

Sirolimus concentration in plasma (ng/ml)

Before After Before After

Results
In 8 patients' oral intake of Sirolimus was tolerated well, no severe side effects were noted. In 1 patient, after 5 months of treatment myocardial hypokinesis was revealed, treatment with sirolimus was suspended. In 1 other patient treatment with Sirolimus was suspended after 5 months, because of scheduled neurosurgical procedure. In 6 patients we noted clinical improvement (e.g., reduction in pain, reduction of swelling and bleeding). In 4 patients we noted volume reduction in control MRI. In 4 patients hyperlipidemia was diagnosed, but diet treatment was sufficient, statins were not required. None of the patients' malformation progressed during therapy.

Discussion and Conclusions
Sirolimus is an option for treatment in patients with complex and massive vascular malformations, which do not respond to standard treatment methods. Treatment is well tolerated with few side effects. In many cases it causes reduction of symptoms and in some reduction of malformation volume. Still more research need to be conducted to clarify the length of this recommended therapy.



opis przypadku

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WSTĘP
Ropień wątroby jest bardzo rzadką, zagrażającą życiu chorobą, powstającą najczęściej w wyniku infekcji bakteryjnej, rzadziej grzybiczej lub zakażenia ameby. Najczęściej występuje u pacjentów z niedoborami odporności.

PREZENTACJA PRZYPADKU
16-letnia dziewczynka zgłosiła się do SOR z powodu dolegliwości bólowych brzucha (prawego podżebrza) nasilających się od ok. 2 tygodni. Od około 3 tygodni infekcja dróg oddechowych (leczona w warunkach ambulatoryjnych z miernąpoprawą). Dotychczas dziewczynka nie była hospitalizowana, wywiad w kierunku chorób przewlekłych ujemny. Przy przyjęciu pacjentka w stanie ogólnym dość dobrym, nie gorączkowała, HR 113/min, RR 112/67. Obserwowano pogarszanie stanu klinicznego pacjentki w trakcie kilku godzin od przyjęcia do szpitala.

DIAGNOSTYKA
- ***WBC, CRP, PCT*** ↑↑↑
- ***Hb 7,2, Hct 22*** ↓
- ***D-Dimery, Fibrynogen*** ↑

USG j.brzusznej: W segmencie VI wątroby, podtorebkowo uwidoczniono hypoechogeniczną nieregularną zmianę, bez widocznego przepływu krwi – jak gęstopłynową o wymiarach 73x58 mm.

Zdj. 1 TK jamy brzusznej z kontrastem – zbiornik płynowy ok. 65x67x92 mm

LECZENIE
Antybiotykoterapia
(Tazocin + Wankomycyna + Metronidazol)

Kwalifikacja do drenażu ropnia

Przeszkórny drenaż ropnia pod kontrolą USG – ewakuowano 120 ml treści ropnej, pozostawiono dren typu Pigtail

Poprawa stanu klinicznego pacjentki, obniżanie parametrów zapalnych

Konsultacje specjalistyczne :
gastroenterologiczna, immunologiczna, endokrynologiczna

Pomimo szerokiej diagnostyki nie udało się ustalić etiologii ropnia

Zdj. 3 Kontrolny RM jamy brzusznej z kontrastem – nieregularny ubytek wątroby 26x19x30 z obrzękiem wokół.

WNIOSKI
Szerokowidmowa antybiotykoterapia w połączeniu z przeszkórnym drenażem ropnia okazały się skuteczną metodą leczenia. Mimo wielospecjalistycznej współpracy, etiologia nie zawsze jest możliwa do ustalenia.

Bibliografia:
1.Waghmare M, Shah H, Tiwari C, Khedkar K, Gandhi S. Management of Liver Abscess in Children: Our Experience. Eurasian J Hepato-Gastroenterol 2017;7(1):23-26.
2.Mishra K, Basu S, Roychoudhury S, Kumar P. Liver abscess in children: an overview. World J Pediatr. 2010 Aug;6(3):210-6. doi: 10.1007/s12519-010-0220-1. Epub 2010 Aug 13. PMID: 20706820.

Most important accomplishments in the 2022/2023 academic year:

- 36 patients were included until march 2023
- All patients were diagnosed with lymphatic malformations
- 2-4 sections (5-10 um thickness) were obtained from parafin embedded tissue blocks from each patient
- In the cooperation with CORE Lab DNA was isolated from obtained tissue
- Search for the PIK3CA gene mutation in hotspots has started – ongoing

Conclusions

- Due to the early stage of the research experiment, it is not yet possible to present the results of the study.
- If the hypothesis is confirmed, it could be possible to use targeted therapy in this group of patients.