CASE 3.

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1. Report of a case

4. Discussion and conclusions
#### Brief case description

| Thirty-one (31) year old male with multiple nodular subcutaneous tumors and aches in his back has been admitted to the University Plastic Surgery Clinic, Medical Faculty, Skopje due to diagnostic surgical biopsy. |
First skin biopsy No. 1130357

Oval skin excision measuring 1.9x0.8cm with SFT measuring 1.1cm has been received for histological analysis.

Standard histological techniques have been used with H&E staining and immunohistochemical analysis for CD4, CD8, CD20, CD25, CD68, MCT.
CASE REPORT
CASE REPORT

Diagnosis

• Chronic lymphocytic vasculitis

Recommendation

• New skin biopsy for DIF analysis, radiographical examination due to a strong aches in the back.
Second skin biopsy No. 1131636: Oval skin excision measuring 2.2x0.3cm with SFT measuring 1.1cm without peculiar features has been received for DIF analysis.

On DIF analysis negativity for IgG, IgM, IgA, C3c, C1q, Fibrin was found. Afterwards standard histological techniques have been used with H&E staining and PAS.
MRI revealed tumor mass in the subcutaneous tissue all over the back of the patient and in the retroperitoneal soft tissue region.
CASE REPORT

- Third core needle biopsy No.1133255: hypocellular colagenous tissue with entraped accumulations from polymorphous cells: lymphocytes, plasma cells, and large amount of histiocytic cells with pleomorphic features;
- some of them with foamy cytoplasm, or eosinophylic cytoplasm and multinuclear giant cells.
- Pseudocysts lined with cells with histiocytic features were found.
Vimentin

S100A4
CASE REPORT

CD10

CD11c
CASE REPORT

CD68
CASE REPORT

Bone marrow biopsy: normal finding

Laboratory analyses: normal range

Molecular analyses: Activating mutation of BRAF V600E (+) (RT PCR).

Diagnosis: Erdheim-Chester disease
The patient has been treated with prednisone 1 mg/kg for one month for lymphocytic vasculitis, and then followed with INF alfa 3 000 000 U/3 times/week for the next three months.

Clinical improvement of the symptoms after 10 days from the beginning of the treatment.

After 3 months a controlled PET CT revealed significant reduction of tumor mass (SUV from 6 to 2.3).

Therapy with α-INF was continued and patient is still in a good clinical condition.
Histiocytic neoplasms are derived from mononuclear phagocytes (macrophages and dendritic cells) or histiocytes.

Dendritic cell tumours are related to several lineages of accessory antigen-presenting cells (dendritic cells) that have a role in phagocytosis, processing, and presentation of antigen to lymphoid cells.

The cellular counterparts of this group of neoplasms consist of:
A) myeloid-derived macrophages;
B) myeloid-derived dendritic cells;
C) stromal-derived dendritic cells.

Histiocytic and dendritic cell neoplasms:

- Histiocytic sarcoma
- Tumours derived from Langerhans cells
- Indeterminate dendritic cell tumour
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumour
DISCUSSION and CONCLUSION

The revised 2008 WHO classification (1) of malignant hematological tumors proposed to assign separate histiocytic proliferations such as:

- **Disseminated juvenile xanthogranuloma**
- **Erdheim – Chester disease**, supposed to origin from interstitial dendritic cells.

The idea to create these provisional entities was to enable to collect new cases for further studies and to maintain the purity of well-defined categories.

DISSCUSSION and CONCLUSION

- Erdheim-Chester Disease (ECD) is a rare form of non-Langerhans' cell histiocytosis.
- Individuals affected by this disease are typically adults between their fifties and seventies years but patients between the ages of 7 to 84 years have been diagnosed.
- Males and females are almost equally affected.

The multi systemic form of ECD is associated with significant morbidity, which may arise due to histiocytic infiltration of critical organ systems.
DISSCUSION and CONCLUSION

- The heterogeneous manifestations of ECD vary amongst different individuals. This results in a presentation that may vary from an indolent focal disease to a life threatening organ failure.
- The most common presenting symptom of ECD is bone pain; additionally general symptoms like fever, fatigue, weight loss and microcytic anemia are also reported.
- Even though the etiology of ECD is unknown, it is thought to be associated with an intense TH1 immune response.
- Abnormal blood vessels proliferation in dermal tissue in our case and lymphocytic vasculitis could support this theory. Nevertheless, these patients are associated with the V600E BRAF mutation, which is estimated between 38% and 68% in most reports.
- In recent report all ECD patients (18/18) had the V600E BRAF mutation.
- This opened a new treatment approach with novel targeted therapy.
DISSCUSION and CONCLUSION

- The diagnostic criteria are based on radiographic and histologic findings.
- On X-ray analysis most of the ECD cases are revealed with bilateral osteosclerotic changes in large bones. Scintigraphy assessment with $^{99m}$Tc in ECD reveals abnormal strong labeling of distal large bone ends that was not a case in our patient.
- CT scans of the lumbar region on two occasions also was negative.
- After MRI of spine and PET CT, a lesion was clearly detected.
DISSCUSSION and CONCLUSION

- Definite diagnosis of ECD is established only once CD14+/CD68+/CD163+/Factor XIIIa+ histiocytes are identified within a biopsy specimen, in opposite to Langerhans cells histiocytosis where the cells are CD1a+/CD207(langerin)+.

- However, in some cases, a mixed disorder arises in which separate lesions have distinct phenotypes or a single lesion has a mixed phenotype.

- Therapy is of limited options.

- Currently, the first line of treatment interferon-α is the most extensively studied agent in the treatment of ECD.

- Treatment with other agents, cladribine (2CDA), anakinra and vemurafenib are currently advocated as promising second line treatments for patients whose response to interferon-α is unsatisfactory.

- Overall, the 5 years survival of ECD is 68%.
CONCLUSIONS

This case highlights the different clinical, radiological and pathological manifestations associated with ECD.

Changes in the blood vessels and skin changes might have some insights on immunological pathogenesis of the disease.

After the diagnosis has been established, the patient showed significant disease regression on PET CT initially and 4 months after starting treatment.

In line for better characterization, in addition to the necessity of the correlation with morphological and immune-phenotypical features of this entity, further studies that would shed new insights on the epigenetic and cytogenetic characteristics of ECD are needed.

We need adequate knowledge and awareness for existing of ECD and that it is obvious to the pathologist.
THANKS FOR LISTENING
ANY QUESTIONS?