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Original Research Paper

Dermatology

VOGT-KOYANAGI-HARADA DISEASE AND PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA: A CASE REPORT

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ABSTRACT Vogt Koyanagi Harada Disease VKHD is a rare central nervous system condition that specifically affects vision and hearing. The disease, with not established etiology, presents with signs and symptoms of a loss of immune tolerance to melanocytes within the meninges, eyes, skin, hair and ears. VKHD is associated with other autoimmune disorders, but still, we don't know an association between VKHD and Primary Cutaneous Anaplastic Large Cell Lymphoma. We present here a case with such association.

KEYWORDS : Vogt Koyanagi Harada Disease, melanocytes, meninges, eyes, skin, hair, ears, Primary Cutaneous Anaplastic Large Cell Lymphoma

Case Report

A 54 years old woman, diagnosed with Vogt Koyanagi Harada Disease on 2015 in Greece and later confirmed in Italy, presented to our department on November 2021 with a history of two months of large necrotic, ulcerative -purulent lesions on lower part of the back, (right inferior lumbar region), and popliteal region, and hyperpigmented and hypopigmented lesions on the trunk and extremities.(Figure 1) The patient was on treatment with AIS and immunosuppressors for years (Prednisolone 20 mg/day and Azathioprine 100 mg/day). Blood tests performed were on normal ranges. Skin specimens from the lesions were send for histopathological examinations for the suspected diagnosis: Pyoderma Gangrenosum, Ulcerative Morphea and Neoplasms Baso - Squamous Carcinoma.

Histopathologic examination confirmed the presence of a neutrophilic infiltration compatible with Pyoderma Gangrenosum.

After this clinicopathological correlation the patient was diagnosed with Pyoderma Gangrenosum associated with VKHD, and the dose of prednisolone was adjusted to 30 mg /day.

The patient was in good recovery and left the hospital. On April 2022 the patient presented to Emergency Department with a history of new painful lesions on the thighs, (Figure 2), fever 38-39 grade Celsius, without any reaction to antibiotics, alterated blood tests: high WBC, low Lymphocytes, low PLTs. Consultations with: surgeon, angiologist, hematologist and CT of lower extremities were performed and femoral abscesses due to immunosuppression was suspected. No presence of any liquid or pus were detected on the lesions during puncture.

We performed other skin specimens of the new lesions and the histopathological examination confirmed High Grade Non-Hodgkin Lymphoma (CD45 +++, Ki67 70 %, CD3+, CD5+, BCl2+++, CD8+). It was difficult for us to perform specific IHC. The final diagnose was Primary Anaplastic Cutaneous Large Cell Lymphoma. The patient died on July 2022, after 2 months of therapy, due to Acute Renal Failure.

Figure

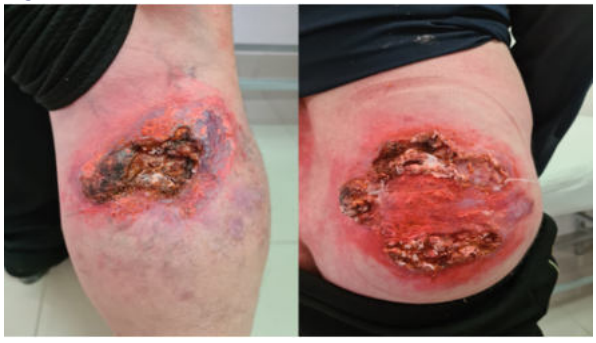

Figure 1: Large necrotic, exudative -purulent ulcerations.

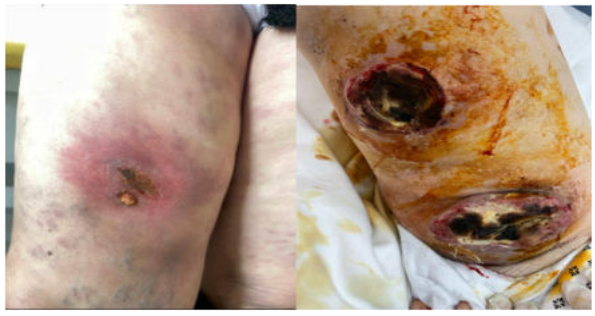

Figure 2: Purulent-necrotic lesions on the thigh

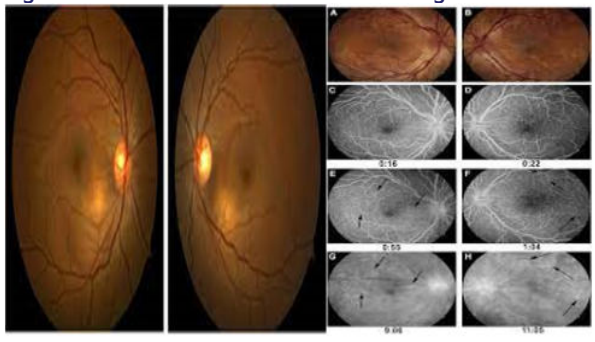

Figure 3: Retinal Detachment

DISCUSSION

Vogt Koyanagi Harada Disease VKHD(Figure 3) is a rare central nervous system condition that specifically affects vision and hearing. The disease, with not established etiology, presents with signs and symptoms of a loss of immune tolerance to melanocytes within the meninges, eyes, skin, hair and ears. The main symptoms: headache, nausea, dizziness, severe eye pain, uveitis, blurry vision, retinal detachment, blindness, areata alopecia and hypo-hyper pigmentations on the skin.

This relatively rare condition has a distinct Phenotypic picture in both its early and late manifestations. Some of the genetic and immunologic facets of VKH have been elucidated due to recent technological advances. VKH syndrome has been associated with certain genetic factors, particularly specific human leukocyte antigen (HLA) genes. The HLA system, also known as the major histocompatibility complex (MHC), plays a crucial role in the immune system by presenting antigens to T cells, thus regulating immune responses.

Several HLA genes have been linked to an increased risk of developing VKH syndrome, with the most prominent associations being HLA-DR4 and HLA-DRB1*0405. These genes are part of the HLA-DR4 serotype, which is found in a higher frequency in individuals with VKH syndrome compared to the general population.

It is important to note that while certain HLA genes increase the susceptibility to VKH syndrome, the disease is believed to result from a complex interplay of genetic and environmental factors. This means that having these HLA genes does not guarantee the development of the syndrome, but it may increase the likelihood of its occurrence when combined with other contributing factors. (Joanne YW Ng et al 2014) The pathogenesis of VKH disease remains uncertain; however, aberrant activation of the Th1 and Th17 pathways in genetically predisposed individuals has been found to be involved in the development of this disease [21]. In a recent study by Zhou et al 2023, found an association between the *PRKCD* rs74437127 and *CARD9*rs3812555 polymorphisms and VKH susceptibility, but also revealed that the increased susceptibility of rs3812555 for VKH may be mediated by regulating *CARD9* gene expression and the production of pro-inflammatory cytokines, such as TNF-α. Thus, SNP rs3812555 identified in this study, as a functional variant, may provide new insight into gene therapy for VKH disease.

Immunologic and genetic factors are recognized to play important roles in the development of VKH disease (Chen et al., 2020; Du et al., 2016; Zhong et al., 2021). Over-activation of Th1 and Th17 cells and deficiency of Treg function are reported in this disease (Du et al., 2016). Genetic variants in a number genes involved in innate and adaptive immune responses confer to susceptibility of VKH disease (Du et al., 2016). Recently, Asakage et al. illustrated 153 upregulated and 35 downregulated miRNAs in VKH patients (Asakage et al., 2020). Furthermore, our group depicted the circular RNA profile of VKH disease and the results showed that circRNAs may play a crucial role in the pathogenesis of this disease (Shu et al., 2021). Despite all of these, current understanding of the pathogenesis of VKH disease is still far from complete.

VKHD is associated with several autoimmune diseases. There are no accurate statistical data for its association with Lymphoma, but in some references published in the literature such as: (Noriyasu Hashida, Shintaro Kanayama, Atsushi Kawasaki & Kenji Ogawa, 2005) ;Annie Mathai MS, Ashish Lall FRCS (, Rajeev Jain MS, Avinash Pathengay FRCS (2006); Kanae Fukutsu, Kenichi Namba,,Daiju Iwata, Kazuomi Mizuuchi, Satoru Kase, Kayo Suzuki, Hiroshi Shimizu, Yukiko Shibata, Fumihiko Yamawaki, Masahiro Onozawa & Susumu Ishida ,2020) it is reported and suspected that VKHD may be the first symptom of a Large Cell Lymphoma.

On the other side there is evidence that the first manifestation of a Large Cell Malignant Lymphoma is retinal detachment. Many authors suspect that some systemic malignant diseases like Anaplastic Large Cell Lymphoma presented with eye diseases, hiding this way their origin and being difficult to diagnose.

Pyoderma Gangrenosum is a rare skin condition with unknown etiology presented with ulcerative lesions that falls into the category of neutrophilic dermatoses. It is associated in 50% with other diseases such: Inflammatory Bowel syndrome, Rheumatoid Arthritis, Leukemia and IgA Monoclonal Gammopathy. There is no data in literature that confirms the association of VKHD with Pyoderma Gangrenosum.

CONCLUSION:

In conclusion this case adds the reported data so far for the coexistence of VKHD with Primary Cutaneous Anaplastic Large Cell Lymphoma, PCALCL.

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