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Research Article

Erdheim-Chester Disease (ECD) is a Rare Histiocytic Neoplasm of Non-Langerhans Cell Histiocytosis

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Abstract

ECD is a rare life-threatening, slowgrowing blood cancer called a histiocytic neoplasm, characterized by infiltration of non-Langerhans cell and by clonal expansion of histiocytes. The unknown etiology of ECD, the wide variety of its clinical features and manifestations that often-mimicking other diseases, lead to the obscure and diagnostically elusive properties of this disorder, and support it classification as a form Langerhans Cell Histiocytosis (LCH). The overproduction of histiocytes (histiocytosis), and xanthogranulomatous infiltration in critical organs leads to inflammation that causing multisystem failure. Histologically, it was observed an infiltration of tissues by sheets of foamy CD68 (+) CD1a (-) histiocytes on biopsy specimen, this finding is critical for definitive diagnosis of ECD. Nevertheless, histiocytes are large phagocytic cells that help fight infection and destroy foreign substances. There are plethora of hypotheses and decades of debate about whether ECD is a neoplastic or immune disorder. Indeed, ECD neither considered a hereditary or contagious disease. In 2016 the World Health Organization recognized ECD as a blood cancer. Molecular findings, cancer-causing DNA mutations in V600E BRAF and other mutations of the MAPK (MARPK1) and PIK3 pathways (NRAS, PIK3CA) altogether pointed to a neoplastic, rather than inflammatory, nature of the disease. Herein, we mustered and overviewed the facts about a panoramic consolidation of all the various events concerning ECD. We shed light also on the upheaval BRAF inhibitors treatment that demonstrate efficacy and gave longer prognosis than expected for our patient. There is a departure from the norm regarding the survival continuity of more than 15 years concerning our patient by Vemurafenib.

Keywords: Erdheim-Chester Disease; Multisystem Disease; Non-Langerhans' Cell Histocytosis; V600E BRAF

Introduction

ECD is neither considered a hereditary or contagious disease [1, 2]. It is a rare life-threatening, orphan multi-systemic disease, with low survival rate for patients at 1 and 5 years are 96% and 68%, respectively [3]. Although ECD affects foremost adulthood typically in middle ages with slight male predominance. The ages of the affected patients range from their 5th and 7th decades of life [4, 5]. Anyway, diagnosis of the illness has been reported between the ages of 7 to 84 years [6] although cases in childhood have been notarized in the medical literature [7-9]. This multifaceted disorder, has diverse clinical combinations of symptoms. It is considered as slowgrowing blood cancer that originates in the bone marrow called a histiocytic neoplasm, characterized by infiltration of non-Langerhans cell and by clonal expansion of histiocytes in different tissues and organs (Figure 1 & Figure 2). These histiocytes cells, penetrate the collagenous connective tissue and cause wide inflammation, as a result, the affected tissue becomes thickened, dense and fibrotic.

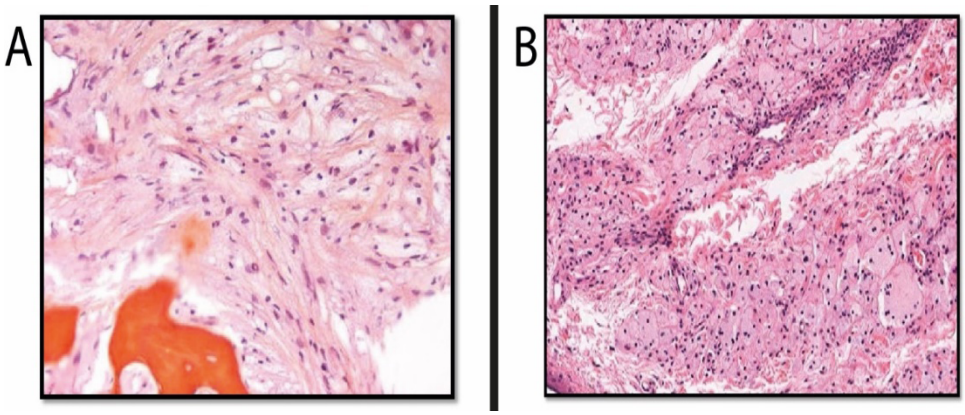

Figure 1: A. Biopsy of the femur: spongy bone tissue in which the medullary spaces are infiltrated by foamy histiocytes within a fibrous stroma (hematein-eosin-saffron, X200). B. Xanthelasma Cells, cutaneous manifestation of lipid laden foamy cells in the epidermis. They manifest as yellowish white plaque like lesions in the eyelid skin, commonly in the medial canthus.

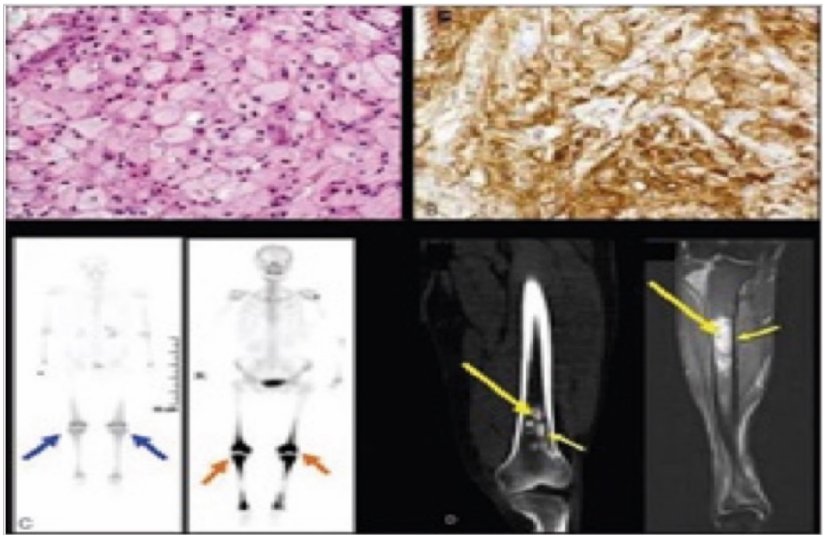

Figure 2: Histopathologic and radiographic findings of ECD. (A) Hematoxylin-eosin–stained biopsy section of ECD lesion revealing lipid-laden histiocytes characteristic of ECD. (B) IHC stain for CD68 revealing positivity of histiocytes. (C) Tc 99m-methylene diphosph, demonstrating symmetric diametaphyseal radiotracer uptake and diffused uptake involving: the long bones of the legs (arrow), elbows, along the distal half of humerus, knees, the distal half of the femur and tibia around the orbital cavity. CT-scan and MRI scan represented respectively in (C) and (D) showing sclerotic lesions of the metaphyses of femur and tibia (arrows). CT = Computed Tomography, ECD = Erdheim–Chester Disease (ECD), IHC = Immune Histochemical. Bowirrat et al., 2016

Epidemiologically, since the first publication in the literature in 1930 by the Austrian pathologist, Jakob Erdheim (1874-1937), and the American pathologist, William Chester (1903-1974) [10], few reported cases were published worldwide.

The incidence of ECD is approximately 1 in a million [11, 12], and the prevalence has not been precisely specified; recently the number of cases estimated to be 1500 cases, which have been reported worldwide in medical literature since the first 2 reported cases of "lipoid granulomatosis," later renamed Erdheim-Chester disease which were described by William Chester in 1930 [13-15].

The Symptomatology of ECD (Figure 3)

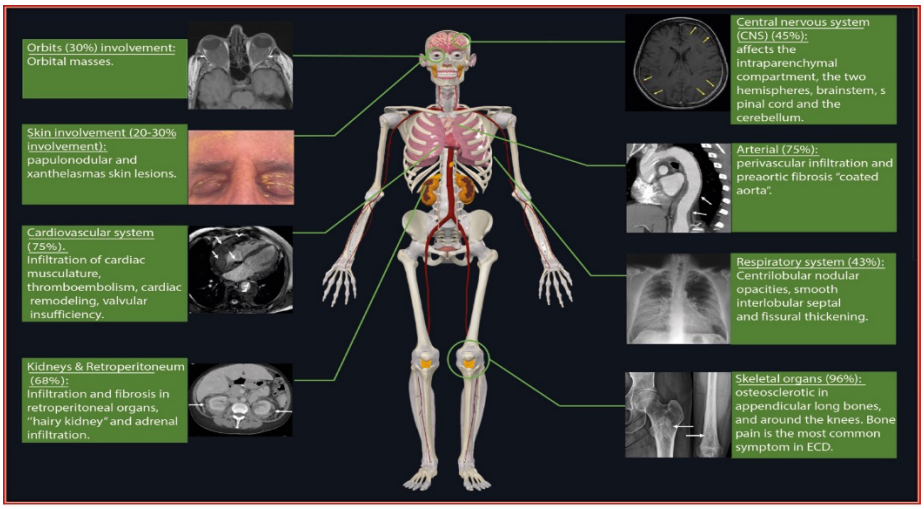

Figure 3: Multisystem involvement in ECD – Clinico-Radiological view. (Bowirrat A, 2023)

1. Skeletal And Extraskeletal Involvement

ECD has an obscure and elusive properties with various clinical spectrum and manifestations, that often mimic other diseases. It can involve any organ of the body from vertex-to-toes, but most commonly affect skeletal and extraskeletal organs 96% vs. 50% respectively [6, 16]. However, Arnaud et al., (2011) reported that 98% of his patients had at least one extra-skeletal feature of the disease [17].

ECD commonly presents with aggressive bone pain, which is the most frequent symptom [18]. Painful waves associated with multifocal and symmetric osteosclerotic lesions of appendicular long bones, particularly around the knees, including the shafts (diametaphyseal) and the shafts converge with the ends (epiphyseal) were reported. Axial skeleton, pelvis, and spinal involvement was also seen.

Osteosclerosis injures, which is the essential hallmark of the skeletal involvement are reported in more than 80% of cases; vertebral cord, cranial bones, rib, facial bones and temporal bone has also been reported [19, 20]. ECD affects critical organs, such as, Central Nervous System (CNS), cardiovascular system, lungs, kidneys (retroperitoneum) and skin. Other body organs may be involved with different degree.

2. Central Nervous System (CNS) Involvement

CNS involvement in ECD is throughout the entire neural axis and affects the two hemispheres, brainstem, spinal cord and cerebellum. Drier et al (2010). reported that 45% of ECD patients, have complains related to CNS and/or orbital manifestations [5]. These manifestations, are classified according to their frequency, were hypothalamic-pituitary axis (leads to diabetes insipidus), retro-orbital lesions (leads to exophthalmos), brainstem and cerebellar involvement of ECD (leads to cerebellar ataxia, pyramidal syndrome [21], cerebellar dysarthria, multidirectional nystagmus, cerebellar dysmetria, hypermetric saccades, negative suppression of the vestibulo-ocular reflex), and to panhypopituitarism and papilledema [5, 22].

Sometimes, CNS involvement represents the only manifestation of the disease. It was estimated that 50% of ECD CNS cases are isolated and responsible for 30% of all deaths because of the poor prognosis. It is worthily to mention, that 50% of the symptomatic ECD CNS injuries located in the intraparenchymal compartment, and cranial neuropathies and ataxia are dominant clinical feature [17, 23].

3. Cardiovascular System Involvement

Relatively ECD affects the cardiovascular system as well as the CNS. Roughly 75% of ECD patients suffer from cardiovascular complications that lead to poor prognosis [24]. Lesions encompasses cardiac insufficiency, cardiac infarction, thromboembolism, cardiac remodeling, valvular insufficiency, cardiac ischemia, infiltration of cardiac musculature (especially

the right atrium-pseudotumor) and peripheral edema. Pericardial histiocytic effusion is the primarily lesion observed, in addition perivascular infiltration and preaortic fibrosis "coated aorta", generally leading to deadly consequences [5, 25].

4. Respiratory System Involvement

43% of ECD patients have pulmonary complications [26]. Classical histiocytic infiltrates in the lung causing interstitial pulmonary disease which represents a definitive diagnosis of ECD. Interstitial pulmonary disease described by centrilobular nodular opacities, smooth interlobular septal and fissural thickening, centrilobular nodular opacities and pleural effusions [17, 27, 28].

Asymptomatic cases were also reported, and are represented in 45-55% of cases, usually pleura region and sometime sinuses are involved. The general symptoms include dry cough, insidious dyspnea, sinus congestion and shortness of breath [29].

5. Kidneys & Retroperitoneum Involvement

Retroperitoneal region is one of the preferred target of histiocytic infiltration in ECD. This region includes all tissues surrounding kidneys and large blood vessels like aorta. Totally, involvement of the retroperitoneal space with ECD was reported in 68% of the patients and the majority are asymptomatic [17, 30]. However, involvement of the kidney leads to renal insufficiency. Abdominal CT scan imaging, appear as "hairy kidney" or "coated aorta". The involvement of the aorta "coated aorta" is associated with infiltration and fibrosis in other retroperitoneal organs, especially, the adrenal gland, renal vasculature, and urogenital system [31].

6. Cutaneous involvement in ECD

Skin involvement in ECD is shown in 20% to 30% patients, with almost 50% of the patients presenting papulonodular and xanthelasmas skin lesions commonly seen as yellowish-orange plaques around the eyes these lesions are usually considered as the initial ECD presentation [32-34]. However, other skin yellowish-brown patches or plaques can be found on the face, neck, armpits, axilla, trunk or groin as well; it may also present as subcutaneous nodules or granuloma annulare-like lesions [34].

The Aetiology and Pathogenesis of ECD (Figure 4)

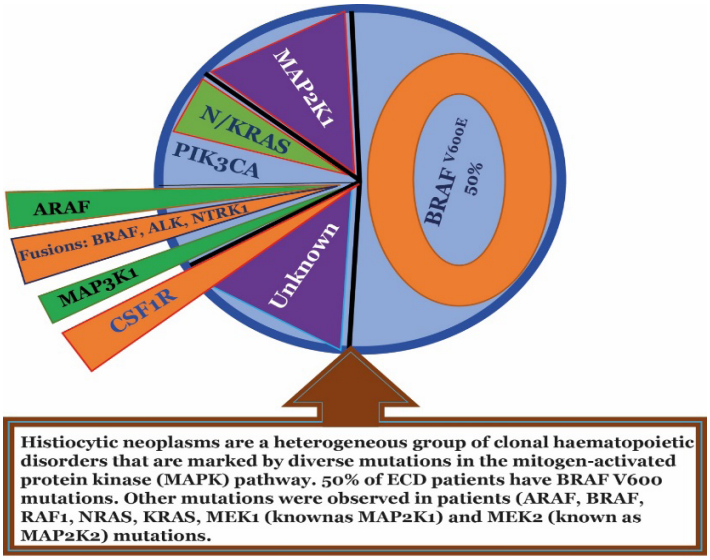

Figure 4: Diverse Gene mutations involved with ECD (Bowirrat A, 2023)

The aetiology and pathogenesis of ECD remain controversial, partially due to scarcity of cases serves as an obstacle in medical science's endeavor to tackle this devastating condition, and even to classify it, as a tumoral or inflammatory disease. However, the pathogenesis of ECD is a subject of debate, with increasing evidence arguing for a clonal neoplastic process versus an inflammatory disease [35-38].

Overproduction of histiocytes (histiocytosis), and xanthogranulomatous infiltration in critical organs leads to inflammation that causing multisystem failure [39]. Pathologically, ECD has xanthomatous lineaments, fibrotic features, and incidental pathognomonic multinucleated cells called "Touton giant cells", characterized by their xanthomata's cytoplasm and their nuclei organized in a wreathlike ring [40-42].

Moreover, it was observed an infiltration of tissues by sheets of foamy CD68 (+) CD1a (-) histiocytes on biopsy specimen, this

finding is critical for definitive diagnosis of ECD. Nevertheless, histiocytes are large phagocytic cells belonging to the immune system that help fight infection and destroy foreign substances. There are plethora of hypothesis and decades of debate about whether ECD is a neoplastic or immune disorder. This dilemma was resolved in 2016 by the World Health Organization who recognized ECD as an inflammatory myeloid neoplasm [43, 44].

The histology of ECD is still inconclusive and ambiguous. Molecular findings, and the recent detection of cancer-causing DNA mutations in V600E BRAF proto-oncogene gene, additional mutations of the MAPK (MARPK1 - Mitogen-activated protein kinase) signaling pathways and PIK3 pathways (NRAS, PIK3CA) were reported. These detections altogether pointed to a neoplastic nature of the illness, rather than inflammatory nature. Indeed, this has been based on the facts that pathological histiocytes both express pro-inflammatory cytokines and chemokines, and harbor activating oncogenic mutations along the MAPK signaling pathway (most commonly the BRAFV600E mutation).

In the last decade, an involvement of BRAF mutations in the pathogenesis of ECD were reported [45]. Recent studies reported an association of somatic BRAF gene mutations in 50% of cases of ECD [46, 47]. BRAF V600E is a somatic mutation, meaning the change in the DNA of the cells occurred during a person's lifetime and is present only in certain cells. Similarly, MAPK (MARPK1 - Mitogen-activated protein kinase) and PI3-AKT pathway somatic mutations and/or fusion genes have been shown to play a significant role in ECD pathogenesis.

Indeed, B-Rapidly Accelerated Fibrosarcoma Gene (BRAF) mutations are also associated with other malignancies, including pulmonary adenocarcinoma, melanoma, papillary thyroid and colorectal carcinomas. The presence of BRAF gene mutations in ECD and other malignancies, strengthens the hypothesis that a clonal neoplastic origin of ECD is present. For this motive, ECD has been classified as a malignancy [45, 46, 48-53].

The Diagnosis of ECD

The heterogeneous clinical manifestations and protean characteristics of ECD, in addition to its scarcity, makes its diagnosis challenging and often requires an integration of Histopathologic features together with clinical, pathognomonic radiological features, depending on biopsy for confirmation, in conjunction, as of recently, genetic finding [3, 54-56].

Diagnosis mainly relies on histological analysis of the affected tissue, which specifically shows xanthogranulomatous infiltrates of foamy CD68 (+) CD1a (-) histiocytes on biopsy specimen surrounded by fibrosis. (Immunohistochemical staining is positive for CD68 and negative for CD1a) [57].

It is worthily to mention, that these histiocytes are non-langerhans with foamy or eosinophilic cytoplasm, which absence birbeck granules, nested within a polymorphic granuloma, fibrosis or xanthogranulomatosis.

Eventually, sophisticated genomic analytic technologies play a critical role in detection of gene(s) mutation involved in the pathogenesis of ECD.

Recently, the discovery and identification of recurrent BRAFV600E mutations which are universally present in ECD. More than 50% of patients testing positive for the BRAF V600E are affected by ECD. This genomic finding provided a path, and possibility to diagnosis of this disease. Thus, BRAF V600E genotyping is required, to check for the BRAFV600E and alterations in the MAPK pathway [45, 47, 58].

Skeletal lesions are almost universally present on imaging. The first action toward a diagnosis of ECD is 99mTc bone scintigraphy and/or conventional radiography. (99)Technetium bone scintigraphy illustrating clear tracer uptake by the lower, upper long bone and pelvic region is highly suggestive of ECD, and a 'hairy kidney' appearance on abdominal CT scan is observed in about 50% of all ECD cases [56, 59].

Additional aid players needed for the diagnosis of ECD are the various radiological techniques. Baseline whole body (vertex-to-toes) FDG-PET-CT, encompassing the lower limbs, is necessary for all patients to aid in diagnosis and describe the expansion of the disease; if FDG-PET cannot be available, or unapplicable, CT scan of the pelvis, abdomen and chest, with gadolinium is recommended as well as imaging of the lower limbs (CT scan, MRI). MRI of the brain and heart is recommended in all patients at diagnosis. Thus, imaging plays a key role in diagnosing ECD.

Differential Diagnosis

The differential diagnosis of ECD requires extended clinical efforts, because the variability of the clinical symptoms and the plethora of various disorders that may share symptoms and findings almost similar to those potentially associated with ECD. The differential diagnosis of ECD includes retroperitoneal fibrosis, Histiocytosis X (LCH), sarcoidosis, neurosarcoidosis, demyelinating disease(MS), amyloidosis, IgG4-related disease, metabolic disorders, mucopolysaccharidosies, Paget disease, Ormond's disease, Cerebro Tendinous Xanthomatosis (CTX), Wegener's granulomatosis, Whipple's disease, Gaucher's disease, Rosai–Dorfman disease, chronic recurrent multifocal osteomyelitis, Takayasu arteritis, primary hypophysitis, cancers and mycobacterial infections and other types of histiocytosis [25, 60-63].

Treatment for ECD

Unfortunately, no magic cure is able to defeat ECD. The aims of the available treatments are to attenuate the syndromes, delay the progression of the illness, to achieve stabilization, in hope to increase survival rates, and to enhance the quality of life. Treatment of ECD depends on the clinical course of the disease. Treatment is individualized and symptom-specific based on disease course, patient's clinical characteristics, disease mutational status, and fitness level. Asymptomatic cases are usually remaining under observation without cure; close follow-up, and repeated imaging like PET scan or CT scan is needed. Symptomatic patients with complains, such as bone pain, cardiac involvement, central nervous system or other organs, necessitate immediate treatment. Due to the variety of symptoms of ECD, early treatment is requested for patients diagnosed, and suffering of symptoms, before this disorder progresses and lead to organ insufficiency.

Recently, the available treatment of ECD has improved dramatically after the discovery of different mutation genes, especially the BRAF V600E mutations involved in the pathogenesis of the disease. Thus, today the treatment approach is divided to two categories [64]:

Targeted and conventional therapies:

A. Main targeted treatments encompass the following options

- BRAF-inhibitors (Vemurafenib, Dabrafenib, Encorafenib): These drugs are typically used as initial management option for patients with BRAF V600E mutation positive ECD. These drugs are Kinase inhibitors, they block the activity of enzymes called "kinases." Kinases are involved in cell signaling, cell growth, and cell division.
- Oral MEK-inhibitors (Cobimetinib, Trametinib, Binimetinib): These drugs are usually used when BRAF-V600E mutation negative for ECD.

B. Main conventional treatments encompass the following options

- Immunotherapy (Interferon-alpha, Peginterferon-alpha): Interferon was the most commonly used treatment for ECD before the introduction of BRAF and MEK-inhibitor therapies and when genetic mutation–targeted therapy is not possible. Interferes with the ability of cancer cells to divide.
- Chemotherapy (cladribine, cytarabine, vinblastine, and methotrexate): Chemotherapy works by slowing the growth of or killing rapidly dividing tumor cells.
- Anti-cytokine therapy (anakinra, canakinumab, tocilizumab, infliximab): These treatments work by reducing the inflammation that is generated by tumor cells.
- Other treatments (steroids, surgery, and radiation): Steroids may be given through the vein or by mouth to reduce inflammation from ECD.

Materials and Methods

Herein we report an extraordinary case study of ECD of a 38-year-old Arab male patient living in Nazareth Metropolitan area after receiving his informed consent, who has been suffering from ECD since 2008 and still survive the disease for more than 15 years with signs of remission of the disease. Brief clinical history, treatment interventions and chain of events and procedures such as (PET-CT and PET-MRI) have been done over the years for our patient's case, prove that the spread and progression of the disease has slowed dramatically.

During the period of years 2008 to 2014, the patient received symptomatic treatments such as NSAID: Ibuprofen (Etopan 400mg), Naproxen (Arcoxia 120mg), Diclofenac (Voltaren 100mg), with incomplete relief of the pain. In 2009 after his diagnosis with Central Diabetes Insipidus (CDI), MRI was done, secondary hypogonadism, with low lab levels of Testosterone, which was contributed to a lesion demonstrated in the hypophysis gland was reported. In 2015 CT scan was done after encountering diffused abdominal pain, the CT scan revealed presence of mesenteric panniculitis and an enlargement of the mesenteric lymph nodes (12 mm) surrounded by adipose tissue, which was confirmed by a laparoscopic biopsy. Due to continue bone pain, we decided to perform bone scan using [(Technetium-99m-Methylene Diphosphate bone scan (99m-Tc-MDP)]. This radioisotope bone scans technique revealed remarkably increased pathologic uptake of Tc-99m-MDP and especially diffused uptake involving the elbow joints bilaterally; the distal half of humerus and the knees surrounds area. Symmetrical increase uptake in distal half of the femur and tibial condyles was shown to be bilateral. Additionally, involvements and enhanced uptake was seen around the orbital cavity.

In (2016) cranial MRI was performed using different techniques (TSET2, Diffusion, Fair, and T1 with and without contrast) and was compared to the previous MRI scan, (Fig. 2 (C and D). Bone scanning was also performed due to the continuous pain in upper and lower extremities, which had demonstrated diffused involvements of both the upper and lower extremities. A bone marrow biopsy was negative. Along with that, rheumatologic screening was negative for all serologic markers, including Rheumatoid Factor (RF), the Human Leukocyte Antigen B27 (HLA-B27), and Anti- Cyclic Citrullinated Peptides (Anti-CCP). Also, complement and inflammatory markers as C - reactive protein (CRP) were all in the normal range. In the light of these development, we conclude that the patient best diagnosis in this stage is ECD. Thus, we describe interferon-α and corticosteroids.

The initial therapeutic dose of interferon-α was 3 to 6 × 106 units subcutaneous 3 times. The outcomes of the interferon-α were insufficient and the treatment was discontinued. We decided to follow the recently discovered treatment of BRAFV600E inhibitors. Indeed, the discovery and identification of recurrent BRAFV600E mutations are universally present in ECD and open the door for genetic investigation for ECD. Thus, molecular analysis for our patient was performed, and the results were positive for the mutations in V600E -BRAF, which is located in more than 50% of patients testing positive for the BRAF V600E proto-oncogen gene. Thus, in 2017 we decided the use the novel strategic BRAF inhibitor treatment for ECD [(Vemurafenib (Zelboraf®) 240mg/2 tab a day)]. In addition, our patient is using (Testosterone undecanoate (Nebido) 1000 mg testosterone/4ml intramuscular injection every two months), and (Desmopressin Nasal Spray, 10 mcg twice a day), these treatments are for [(testosterone replacement to treat problems caused by a testosterone deficiency (hypogonadism)] and for (treatment of central diabetes insipidus) respectively.

Patient follow up 2017-2023

In 2017, PET-CT with intravenous FDG contrast (mCi10 FDG I cc100) for whole body was performed. In 2018, PET-CT with FDG contrast (11.00mCi of FDG I 100.00cc) and PET-MRI were performed for whole body. In 2020, PET-CT with FDG contrast (4.10mCi of FDG I 80.00cc) and PET-MRI were performed for whole body. In 2021, PET-CT with FDG contrast (4.10mCi of FDG I 81.00cc) and PET-MRI were performed for whole body.

Results

The results of the imaging and treatment are as follow: 2017-2023

In 2017, PET-CT with intravenous FDG contrast (mCi10 FDG I cc100) for whole body was performed: No pathological absorptions of contrast were observed; in brain, neck-with no enlarged lymph nodes were demonstrated, chest, abdominal regions but pathological absorption was observed only in proximal and distal long bones (Figure 5).

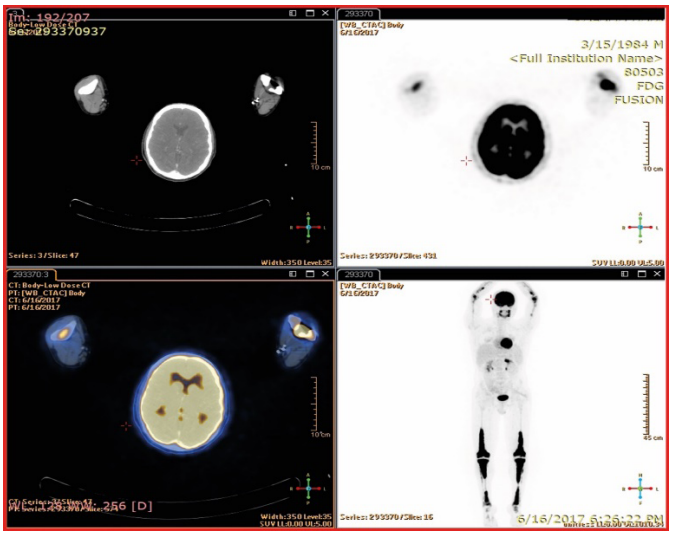

Figure 5: PET-CT with intravenous FDG contrast (mCi10 FDG I cc100) – 2017- for whole body was performed: No pathological absorptions of contrast were observed in brain, neck-with no enlarged lymph nodes were demonstrated, chest, abdominal regions but pathological absorption was observed in proximal and distal long bones of upper and lower extremities.

In 2018, PET-CT with FDG contrast (11.00mCi of FDG I 100.00cc) and PET-MRI were performed for whole body (Figure 6 A,B,C). No pathological absorptions of contrast were observed in different organs; also, abdominal regions were free but little pathological absorption were observed in proximal and distal long bones, and a significant improvement was shown and low absorptions were observed in both upper extremities and fibula bones. Practically no pathological absorption of FDG, whereas in the tibial bones there is an improvement mainly in the distal third.

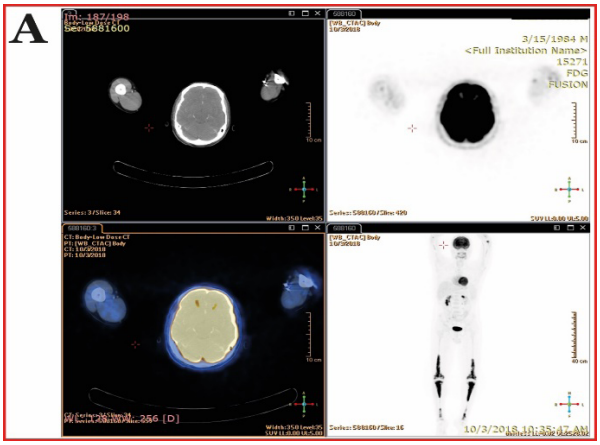

Figure 6-A: (2018 - PET-CT)

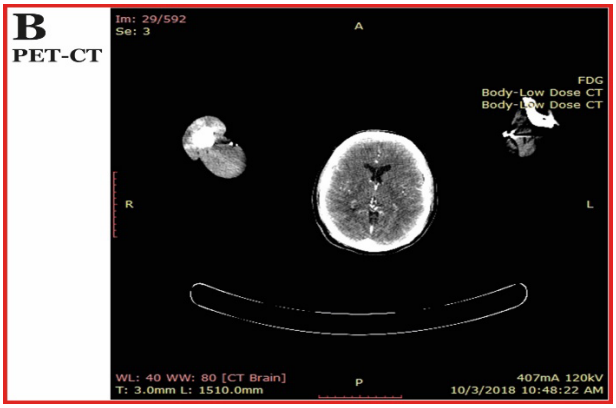

Figure 6-B: (2018 - PET-CT)

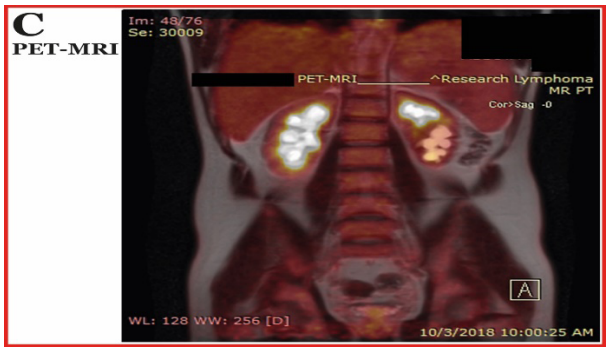

Figure 6-C: (2018 – PET-MRI)

Figure 6 (A, B, C): In 2018, PET-CT with FDG contrast (11.00mCi of FDG I 100.00cc) and PET-MRI were performed for whole body. No pathological absorptions of contrast were observed; in brain, neck-with no enlarged lymph nodes were demonstrated, chest, abdominal regions were free but little pathological absorption were observed in proximal and distal long bones, and a significant improvement in both upper extremities and fibula bones. Today, there is practically no pathological absorption of FDG, whereas in the tibial bones there is an improvement mainly in the distal third.

In 2020, PET-CT with FDG contrast (4.10mCi of FDG I 80.00cc) and PET-MRI were performed for whole body (Figure 7 A&B). Still, no changes as described in 2018, no pathological absorptions of contrast were observed; in brain, neck-with no enlarged lymph nodes were demonstrated, chest, abdominal regions were free. There is practically little pathological absorption at lowest intensity in known lesions in the distal femur, the proximal tibia and the distal tibia. There is no pathological absorption in the arms and fibulas. The skeletal texture in CT without significant change compared to the previous test (2018). In summary, metabolic improvement was observed, but still active disease in the lower extremities.

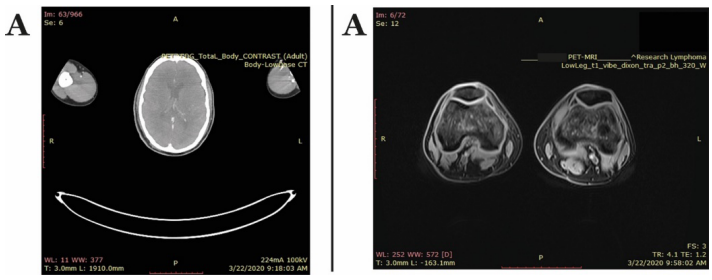

Figure 7A: (2020- PET-CT).

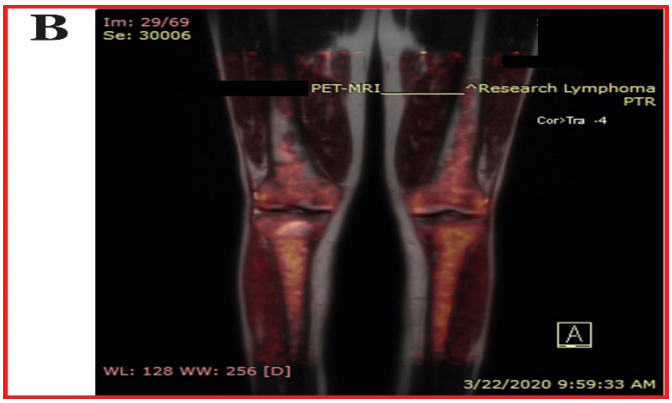

Figure 7B: (2020 PET-MRI).

Figure 7(A & B): In 2020, PET-CT with FDG contrast (4.10mCi of FDG I 80.00cc) and PET-MRI were performed for whole body. Still, no changes as described in 2018, no pathological absorptions of contrast were observed; in brain, neck-with no enlarged lymph nodes were demonstrated, chest, abdominal regions were free. Today, there is practically little pathological absorption at lowest intensity in known lesions in the distal femur, the proximal tibia and the distal tibia. Today, there is no pathological absorption in the arms and fibulas. The skeletal texture in CT without significant change compared to the previous test (2018). In summary, metabolic improvement was observed, but still active disease in the lower extremities.

In 2021, PET-CT with FDG contrast (4.10mCi of FDG I 81.00cc) and PET-MRI were performed for whole body (Figure 8 A&B). The reason for the referral: mixed histiocytosis comparing to the previous referral on (2020). We have observed high absorption of FDG in the muscles, maybe as result of lack of fasting as requested. Still, no changes as described in 2020, no pathological absorptions of contrast were observed; in brain, neck-with no enlarged lymph nodes were demonstrated, chest, abdominal regions were free. Very low pathological absorption in known lesions in the skeleton. The skeletal texture is without changes comparing to the previous referral. In summary, metabolic improvement was observed in whole skeleton.

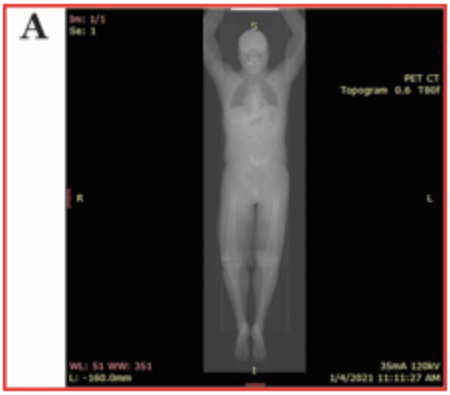

Figure 8A: (2021, PET- CT)

Figure 8B: (2021, B-PET-MRI)

Figure 8: In 2021, A -PET-CT with FDG contrast (4.10mCi of FDG I 81.00cc) and B- PET-MRI were performed for whole body. The reason for the referral: mixed histiocytosis comparing to the previous referral on (2020). We have observed high absorption of FDG in the muscles, maybe as result of lack of fasting as requested. Still, no changes as described in 2020, no pathological absorptions of contrast were observed; in brain, neck-with no enlarged lymph nodes were demonstrated, chest, abdominal regions were free. Today, very low pathological absorption in known lesions in the skeleton. The skeletal texture is without changes comparing to the previous referral. In summary, metabolic improvement was observed in whole skeleton.

In 2023 till now, our patient live natural life, without unusual complains, such as bones pain or other systemic complains. His activity of daily living is intact, but the only complains that bother him are the diabetes insipidus and especially the hypogonadism. The disturbing symptom of low Testosterone level, had a negative psychological consequence, especially on his sexual abilities. Otherwise, the quality of life of our patient increase through the years dramatically after receiving the treatment with BRAF-inhibitors.

Discussion/Conclusion

ECD is quite heterogeneous phenomenon, with incongruous symptoms, dissimilar etiologies and different survival rate. Indeed, despite the scarcity of cases and scientific research related to ECD, the majority of research has been unanimous that about 60% of patients succumb to their disease within 32 months of presentation [3,6], whereas only 9% of ECD patients have succumbed after a median follow-up of 4 years [65]. Various medications have been attempted for ECD [66, 67]. At the forefront of these medications was the traditional corticosteroids which were used to relieve symptoms, sometimes their effectiveness is only transienty effective [68].

Plethora of hypothesis and decades of debate about whether ECD is a neoplastic or immune disorder were reported in the scientific literature. This dilemma was resolved in 2016 by the World Health Organization who recognized ECD as an inflammatory myeloid neoplasm. This discovery reinforced the conclusion comes after the recent detection of cancer-causing DNA mutations in V600E BRAF proto-oncogene gene, and mutations of the MAPK (MARPK1 - Mitogen-activated protein kinase) signaling pathways and PIK3 pathways (NRAS, PIK3CA) in the pathogenesis of ECD [45, 56]. In spite of, the improvement of the different sophisticated technologies such as (Imaging and molecular testing), and increase our understanding of the underlying pathogenesis of ECD, more efforts should be invested on the early diagnosis, emphasizing the need for extended clinical investigation and evaluation in adulthood patients coming with unexplained syndromes, especially articular disease associated with pain. Understanding the genomic architecture of the disease and knowing the mutation types help chose the appropriate cure. We highlight the importance of collaboration by a multidisciplinary specialist who should work in concert for the successful treatment. Thus, sharing information and experiences are warranted.

Herein we describe the successful treatment of our patient with ECD with BRAF-inhibitors (Vemurafenib): This drug is typically used as initial management option for patients with BRAF V600E mutation in the tumor cells. BRAF-inhibitors (Vemurafenib) (Zelboraf®) is a Kinase inhibitors, it blocks the activity of enzymes called “kinases.” Kinases are involved in cell signaling, cell growth, and cell division. The medication tablet of 240mg is given two times a day. Thus, we shed light on the upheaval BRAF inhibitors treatment that demonstrate efficacy and gave longer prognosis than expected for our patient. There is a departure from the norm regarding the survival continuity of more than 15 years concerning our patient by using BRAF inhibitor (Vemurafenib). Our patient quality of life increases dramatically. Metabolic improvement was observed in whole skeleton and signs of remission of the disease is also observed and are illustrated by up imaging (Figure 5-8).

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