Case Report
Volume 14:01, 2024

Journal of Clinical Case Reports

ISSN: 2165-7920 Open Access

Atypical Neurological and Gastrointestinal of Undifferentiated Systemic Rheumatic Disease/Overlap Syndrome Responded to JAK2 Inhibitor

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Abstract

A 55 year old female patient, born in the Middle east and living in North America since the age of 12, has been suffering from multiple complex medical disorders. These include history of seronegative Juvenile Rheumatoid Arthritis (JRA), Raynaud Phenomenon, Ulcerative Colitis (UC), severe Endometriosis with multiple excisions and ablation of endometriotic lesions and total abdominal hysterectomy with a Bilateral Salpingo-Oophorectomy (TVH/BSO), Gastroesophageal Reflux Disease (GERD), episodes of Interstitial Cystitis (IC), history of dysequilibrium and vertigo diagnosed as Vestibular Migraine and Persistent Postural-Perceptual Dizziness (PPPD), Hashimoto thyroiditis, fibromyalgia, migratory polyarthropathy, and kidney disease. The patient was treated with a trial of Janus Kinase 2 (JAK2) inhibitor. She responded well to the treatment and has seen significant improvement in her complex GastroIntestinal (GI), neurological, rheumatological, urogenital, kidney and thyroid clinical manifestations. This is a strong indication that many, if not all, of the patient's medical manifestations had an underlying immunological origin.

Keywords: PPPD • Undifferentiated systemic rheumatic disease • Neurological disease • Dizziness • Vestibular migraine • Fibromyalgia • Behcet's disease • TNF alpha • JAK 2 Inhibitor • Overlap syndrome

Introduction

A female patient suffered from an early age from nausea, migraines, GI upsets, joint pains, dactylitis, eye irritations, oral and vaginal ulcers, morning stiffness, Raynaud, on and off low grade fever, dysmenorrhea, pelvic and lower back pain, vaginal burning, GERD, IBD (Inflammatory Bowel Disease), and IC. As she got older her symptoms worsened, and in addition she suffered from acute vertigo and dizziness, hearing loss, fibromyalgia, dermatological issues, seizures, hypertension and tachycardia, Hashimoto thyroiditis, anxiety, as well as kidney disease. All of her medical manifestations were addressed, organ by organ, by different specialists, and at different stages of her life. Whether all these complex medical issues could have a common underlying casue, however, was never considered.

Case Presentation

Juvenile arthritis

In her early teens, the patient became symptomatic in her large joints. She suffered from swelling and pain in her Acromio Clavicular (AC) and knee joints bilaterally, and was diagnosed with seronegative JRA [1]. She received multiple steroid intraarticular injections. These injections alleviated her symptoms temporarily. In addition, she started experiencing various extraarticular symptoms.

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Received: 15 December, 2023; Manuscript No. jccr-23-122869; **Editor Assigned:** 18 December, 2023; PreQC No. P-122869; **Reviewed:** 03 January, 2024; QC No. Q-122869; **Revised:** 09 January, 2024, Manuscript No. R-122869; **Published:** 16 January, 2024, DOI: 10.37421/2165-7920.2024.14.1588

GI involvement

In her late teens, the patient was diagnosed with UC [2] after episodes of lower gastrointestinal bleeding, confirmed with colonoscopy and biopsy. The area of involvement was up to 60 cm of the left colon. Multiple biopsies ruled out the presence of the Crohn's disease. She was treated with 5- Amino Salicylic Acid (5-ASA), 200 mg three times a day, and steroid rectal enema for flare-ups [3]. Episodes of rectal bleeding continued into her late 20s. In her late 30s, multiple routine follow-up colonoscopies were consistent with no ulceration and she was advised to stop her 5-ASA. Since then, her colonoscopies only revealed patchy areas of colitis (confirmed with biopsies) in the left colon area but no ulceration.

In addition, she has been suffering from severe GERD, confirmed with 24 hours PH assays and multiple Esophago gastro duodenoscopies, complicated with Peptic Ulcer Disease. Many biopsies of the stomach and esophagus denied the presence of the Helicobacter Pylori infection. As a result, the patient has been treated with different types of Proton Pump Inhibitors (PPIs) at the maximum dose, including Lansoprazole, Dexlansoprazole and Esomeprazole.

Furthermore, over the years, the patient developed significant intolerances, allergies and maldigestions toward many food products (such as fibers, gluten, dairy and soy protein) as well as allergies toward medications (Table 1).

She continuously suffered from bloating, nausea, and epigastric pain. She underwent many digestive health studies that ruled out conditions such as gastric motility disorders and Small Intestine Bacterial Overgrowth Syndrome. The patient was also negative for celiac disease. She was empirically treated with multiple courses of Xifaxan antibiotic to no effect. High doses of different kinds of probiotics were ineffective. It was also recommended that the patient follows many types of food diets such as FODMAP diet, but the patient did not experience any improvements from her GI symptoms. As such, the patient's diet for many years was limited to rice, potato, and meat. Other symptomatic interventions, including Gabapentin or Tri Cyclic Antidepressants (TCAs), did not help the patient's GI symptoms and carried significant side effects.

Urogenital involvement

Since puberty, the patient suffered from severe dysmenorrhea, pelvic and lower back pain, and vaginal burning. In her 20s, she was diagnosed with

Table 1. Patient's allergies to food and medications.

Food Allergies	Food Sensitivities	Medication Allergies
Peanut Butter	Beans	Opiates
Eggs	Sesame	Sulfacetamine
Almonds	Broccoli	Scopolamine
Gluten	Onions	Sulfonamid Antibiotics
Soy	Scallion	Nortriptyline
Dairy	Potatoes	Iodine (CT Contrast)
Carrot	Pea Protein	Ecklonia Kurome
All peppers	Tomatoes	Serotonin
Radish	Zucchini	Serotonin 5ht-3 Antagonists
Yam	Avocado	Sutures (plastic)
Sweet Potatoes	Imitation Crab	-
Mulluscs	Oyster	-
Salmon	Cumin	-
Iodine	Ginger	-
Flavoring Agents	All Gums (such as Guar Gum)	-
Preservatives (benzoates)	Sulphur dioxide	-
MSG	Sulfites	-
Ginger	Legumes (such as chickpeas)	-
-	Nitrates and Nitrites	-

extensive Endometriosis [4]. She was treated with oral Estrogen-Progestin and Gonadotropin Releasing Hormone (GnRH) analogs (Leuprolide) with no improvement and extensive side effects. She underwent multiple excision and ablation of endometriotic lesions and in her mid-30s, a TVH/BSO. She was not placed on Hormone Replacement Therapy after TVH/BSO due to possible risk of relapse.

Concurrently, the patient developed severe symptomatic IC [5], manifested by persistent Bladder Pain Syndrome. She did not respond to numerous interventions including pharmacological therapies such as Amitriptyline, Pentosan polysulfate sodium, antihistamines and Gabapentine. Multiple Bladder hydrodistension with intravesical therapies to target the Hunner lesions with local anesthetics (such as Lidocaine, Bupivacaine, Capsaicin) Glycosaminoglycans (both heparin and hyaluronic acid), sodium bicarbonate and Dimethylsulfoxide were ineffective [6-8]. The patient also underwent years of pelvic floor physical therapy and was advised to consume a diet low in oxalate [9]. However, none of the above recommendations gave the patient any relief from IC.

Mucocutaneous lesions

Since the onset of the patient's polyarthritis she has had significant episodes of painful oral and vaginal lesions. The oral lesions were aphthous ulcerations in nature (canker sores), multiple and extensive, ranging from a few millimeters to 1 cm. The healing course for the oral ulcers with surrounding erythema ranged between 2-4 weeks. Treatment with topical Triamcinolone paste has been very effective for her oral ulcers. The urogenital lesions, very similar to her oral aphthae, did not respond to any topical treatments including Colchicine.

During the course of her disease, the patient has developed large areas of patchy distribution and hyperpigmented lesions associated with severe pruritus (Figure 1). It has been treated empirically with topical high-potency steroids, intra-lesional steroid injections, and topical anti-fungal medications to no effect. Her biopsy was consistent with localized cutaneous amyloidosis [10].

Neurological involvement

Starting in her late 30s, along with other musculoskeletal and GI symptoms, the patient started experiencing multiple episodes of sudden vertigo, periodic dizziness, dysequilibrium, severe neuropathic symptoms with tingling and burning sensations in lower extremities, sleep impairment with insomnia, and multiple episodes of Hypnic jerks and Restless Legs Syndrome [11]. Her neurological symptoms worsened over time and became persistent dysequilibrium and dizziness, impairing her balance and mobility.

Due to her persistent dizziness and vertigo, the patient underwent extensive ENT assessments. Peripheral vestibulopathy was ruled out. She was diagnosed with Vestibular Migraine and/or PPPD [12]. Empirical use of antihistamines, systemic steroids, Selective Serotonin Reuptake Inhibitors, Serotonin and Norepinephrine Reuptake Inhibitors, Gamma-Aminobutyric Acid analogs, and Benzodiazepines proved ineffective with numerous side effects. Long term cognitive behavioural therapy and extensive Vestibular Therapy were also ineffective.

Multiple CT-Scans and MRIs of patient's brain and ears were normal except for extensive opacification of the left-sided mastoid air cells. The ENT and Neurology teams could not determine the cause, nor did they diagnose it as chronic mastoiditis. No specific treatment was recommended for this issue. It was also determined that, over a period of a year, the patient had lost 30% of her left ear hearing.

Thyroid disease

In her early 50s, the extent of the patient's Rheumatological and Neurological symptoms amplified. She experienced generalized fatigue, hair loss, brittle nails, increased sensitivity to cold and hot temperatures, dry skin, heart palpitations, labile hypo, and hypertension. In endocrinological evaluation, all tests for Pheochromocytoma, including 24 hours urine fractionated metanephrines and catecholamines, were normal. Her TSH fluctuated between normal range to subclinical hypothyroidism level, but her Anti-TPO was constantly on the high side (Table 2).

She was diagnosed with Hashimoto thyroiditis [13]. The ultrasound of the thyroid gland was normal. The patient was put on a low-dose of synthetic thyroxine T4 therapy. However, thyroxine therapy did not resolve her medical symptoms and also caused her severe palpitation and labile hypertension and had to be stopped.

Chronic kidney disease

In her 50s, with the peak of neurological, rheumatological and GI manifestations, the patient's Glomerular Filtration Rate (GFR) started to decline from normal to Chronic Kidney Disease (CKD) stage 3 level [14] (Table 3). Her kidney's ultrasound was consistent with a bilateral increase in echogenicity. The cause of her Interstitial Nephritis was hypothesized to be due to immunological or pharmacological reasons. The patient had consumed many years of proton pump inhibitors to manage her GERD and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) to manage her extensive pains.

Rheumatological manifestations

As discussed above, the patient's rheumatological symptoms initially started with seronegative JRA in her teens. Throughout her life, she experienced asymmetric migratory joint pain and effusion in large joints, distal

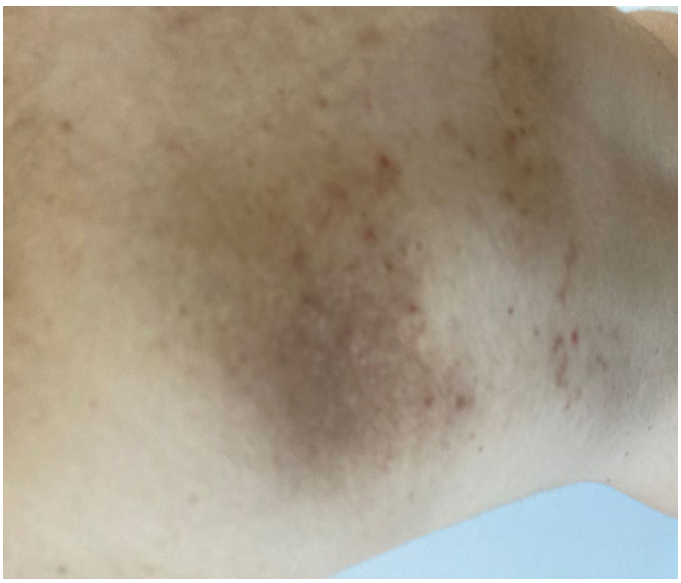

Figure 1. Patient has developed large areas of patchy distribution and hyperpigmented lesions diagnosed as cutaneous amyloidosis.

Table 2. Thyroid functions.

Date	TPO Antibody (IU/mL)
9/30/20	>900
11/28/20	>900
1/23/21	>840
3/30/21	>728
9/20/21	331
1/07/22	341
11/07/22	247

Normal TPO antibody should be <9 IU/mL.
The yellow shade: Patient was on Humira.
The green shade: Patient was on Rinvoq.

Date	TSH (uIU/mL)	Free T3 (pg/mL)	Free T4 (ng/dL)
9/02/15	1.96	-	-
9/10/16	2.98	-	-
6/29/17	3.09	-	-
12/16/19	3.24	-	1.4
7/23/20	6.54	-	1.2
11/28/20	3.72	2.4	1.0
1/23/21	2.23	-	-
9/20/21	2.85	2.4	1.0
1/07/22	4.60	-	0.90
11/07/22	1.80	-	0.77
5/19/23	2.63	2.14	0.83

Patient started Humira on 10/22/2020 and Rinvoq on 4/6/2022. TSH standard range is 0.34-4.82 ulU/mL. Free T3 standard
range is 2.30-4.20 pg/mL. Free T4 Standard range is 0.59-1.61 ng/dL.
The yellow shade: Patient was on Humira.
The green shade: Patient was on Rinvoq.

Table 3. Kidney functions.

Date	Creatinine (mg/dL)	eGFR (Cmnt)
7/11/12	0.90	-
11/4/14	1.10	-
8/10/16	0.91	75
9/21/18	1.12	57
3/28/19	1.10	59
9/30/20	1.15	55
11/28/20	1.35	45
12/16/20	1.06	60
1/23/21	1.15	55
3/30/21	1.12	56
5/14/21	1.27	48
9/20/21	1.15	54
1/07/22	1.13	55
2/08/22*	0.98*	66*
4/06/22*	0.94*	69*
5/07/22	1.13	58
9/01/22	1.24	52
9/20/22	0.97	-
2/16/23	1.10	60
5/19/23	1.00	67

Patient started Humira on 10/22/2020 and Rinvoq on 4/6/2022. Creatinine normal range is 0.40-1.00 mg/dL. Standard range for EGFR is >60 See Cmnt. *From 2/1/22 to 4/6/22 the patient was on prednisone.
The yellow shade: Patient was on Humira.
The green shade: Patient was on Rinvoq.

interphalangeal joints, thumb bases, proximal interphalangeal joints, and second and third metacarpophalangeal joints. On a daily basis, the patient experienced more than 30 minutes of morning stiffness. At the same time, she had symptoms of axial Spondyloarthritis (axSpA) with pain in Sacroiliac joints and spine area with limited range of motion of the lower spine area, enthesitis and dactylitis. Additionally, the patient had been suffering from severe Raynaud phenomenon [15] and fibromyalgia [16] since her teen years. These symptoms magnified in her late 40s. Multiple Rheumatologists evaluated her. Table 4 indicates the patient's inflammatory markers and Table 5 indicates the patient's immunological markers.

The first Rheumatologist impression was that the patient suffered from Systemic Lupus Erythematosus (SLE) [17] due to an elevated AntiNuclear Antibodies (ANA) (320 with IF) (Table 5). However, the rest of her tests were normal. She was prescribed Hydroxychloroquine, which she could not tolerate due to severe side effects. Later she was put on systemic oral steroids, but they were also stopped due to severe GI side effects, worsening headaches and dizziness.

In her early 50s, the patient was extremely sick. She could no longer work. She lost a lot of weight (over 10kg from 58kg to 48kg), could not perform her routine functions, and was in agonizing pain. Therefore, another Rheumatologist was consulted. The second Rheumatologist did not agree with the diagnosis of SLE. It was suggested that the patient suffered from a subtype of Spondyloarthropathy (SpA) [18], or IBD arthropathy (given her history of UC and significant GI disturbances) [19-22], or Undifferentiated Systemic Rheumatic Disease (USRD) [23], or the Overlap Syndrome [24]. Consequently, she was put on a Tumor Necrosis Factor (TNF) alpha inhibitor therapy [25-27], Adalimumab (Humira, 40 mg every two weeks). TNF alpha inhibitors are human monoclonal antibodies (thus called biologic disease modifying agents). The patient responded relatively well after the second dose of Adalimumab and reported a 50% reduction in her rheumatological symptoms, vertigo, dizziness and neuropathy. However, Adalimumab provided only minimal improvement in her GI disturbances. During TNF alpha therapy, the patient still had flare-ups of her joints pain and was put on and off on Prednisone therapy.

After six months of treatment, the effect of Adalimumab got lessened, and her dose was increased to a weekly basis and even a higher dose to no effect. After multiple consultations with different Rheumatologists it was

Table 4. Inflammatory markers.

Date	Sedimentation Rate (ESR) (mm/hr)	C-Reactive Protein (mg/dL)
7/11/12	Normal (28)	Normal (0.3)
6/29/17	Normal (11)	Normal (0.2)
9/18/18	Normal (19)	Normal (0.2)
3/28/19	Normal (29)	High (1.2)
11/28/20	Normal (17)	High (4.1)
9/20/21	Normal (29)	High (3.4)
1/07/22	High (33)	High (5.2)
2/8/22	Normal (29)	High (8.1)
4/6/22	Normal (28)	High (18.9)
7/15/22	Normal (16)	Normal (1.0)
1/9/22	Normal (11)	High (2.9)
5/19/23	Normal (8)	High (2.9)

Normal range for ESR is 0-31 mm/hr and for C-Reactive Protein is <0.9 mg/dL.
The yellow shade: Patient was on Humira.

Date	C3	C4
9/17/18	Normal	Normal
12/14/18	Normal	Normal
3/28/19	Normal	Normal
10/08/20	Normal	Normal
11/28/20	Normal	Normal
1/23/21	Normal	Normal
9/20/21	Normal	Normal
11/28/20	Normal	Normal
1/23/21	Normal	Normal
9/20/21	Normal	Normal
5/19/23	Normal	Normal

Table 5. Immunological markers.

Date	Test	Results
7/11/12	ANA	Positive
8/31/17	ANA	Negative
8/31/17	Rheumatoid factor	Negative
9/17/18	Rheumatoid factor	Negative
9/17/18	ANTI-ds-DNA	Negative
9/17/18	ANTI-La Antibody	Negative
9/17/18	ANA	Negative
12/17/18	ANTI-ds-DNA	Negative
3/28/19	ANTI-RNP Antibody	Negative
3/28/19	ANTI-Sm Antibody	Negative
12/16/19	ANTI-ds-DNA	Negative
9/30/20	ANA	Positive
9/30/20	Cardiolipin AB (IGG)	Negative
9/30/20	Cardiolipin AB (IGG)	Negative
9/30/20	NMDAR1 AB, CBA	Negative
9/30/20	AMPAR2 AB, CBA	Negative
9/30/20	LGI1 AB, CBA	Negative
9/30/20	AMPAR1 AB, CBA	Negative
9/30/20	GABABR AB, CBA	Negative
9/30/20	CASPR2 AB, CBA	Negative
2/08/22	ANA	Negative
2/08/22	JO-1 Antibody	Negative
2/08/22	SCL-70 Antibody	Negative
2/08/22	Centromere B ANT	Negative
2/08/22	B2 Glycoprotein I (IGG)	Negative
2/08/22	Cardiolipin AB (IGA, IGG, IGM)	Negative
2/08/22	DRVVT Screen	Negative
2/08/22	Cryoglobulin	Positive

determined that the patient had developed antibody against Adalimumab [28,29]. Their suggestion was switching her to a different type of TNF alpha inhibitor or starting a new agent such as JAK2 inhibitor therapy [30,31]. To prevent further antibody development against a biologic agent the decision was to start the patient on a JAK2 inhibitor therapy called upadacitinib (Rinvoq at 15 mg/day). Probable diagnosis was non-radiological axial spondyloarthritis *vs*. IBD arthropathy.

After taking Rinvoq for three months, the patient reported having a reduction of approximately 60% in her symptoms, including vertigo, dizziness, joint and muscle pains, headaches, fatigue, IC, GI pain, acid reflux, numbness and tickling in her extremities, neuropathy, mouth and genital ulcers, inflamed eyes, and tinnitus. After six months, the patient reported a decrease of approximately 80% in her symptoms. After years of being unable to eat due to severe GI pains, the patient started eating a normal diet, including fibers and many of the foods she used to be intolerant to. After years of weight loss, she started gaining weight (over 10 kg). She also reported having fewer flare-ups and much better sleep patterns after years of insomnia. She experienced fewer Hypnic jerks. After a year of being on Rinvoq, the patient reported a reduction of 95% of her symptoms. Her kidney function and TPO Antibody level both improved significantly after the treatment (Tables 2 and 3). And she no longer needed Prednisone therapy in conjunction with JAK2 inhibitor to address relapses.

Results and Discussion

The complexity of this patient's diagnosis lies in the fact that she suffered from numerous, highly intricated medical conditions involving multi organs. And by the fact that all of her medical manifestations were address organ by organ by different specialists. For example, her UC was address at an early age with 5-ASA. Derivatives of 5-ASA are anti-inflammatory drugs that help to reduce symptoms of ulcerative colitis by blocking the activity of cyclooxygenase and lipoxygenase, thereby reducing the production of prostaglandins [2,3]. But, at the same time, she was suffering from seronegative JRA, GERD, IBD, endometriosis, IC, Raynaud, localized cutaneous amyloidosis and fibromyalgia. Each of these clinical expressions, in her different body parts, was address separately either by pharmacological means or surgical interventions. However, the patient would have benefited immensely if all of these symptoms were considered to have a shared underlying cause.

As the research in the area of immunological disorders expands, it is more and more clear that many of such conditions have an underlying rheumatological origin. As an example, SpAs [18] are a family of joint disorders, which include IBD associated arthritis (or IBD arthropaty) [19-22], Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), reactive arthritis, and undifferentiated SpA. Patients with SpA often present with inflammatory joint pain characterized by morning stiffness lasting more than one hour and improving with activity [18].

The most common extraintestinal manifestation of IBD is arthritis. Arthropathy associated with IBD is a type of SpA with axial and/or peripheral joint manifestations and a negative rheumatoid factor [20]. The peripheral arthritis is mostly non-erosive and may correlate with intestinal disease activity. Axial arthritis can include ankylosing spondylitis, inflammatory back pain, or sacroiliitis and does not always correlate with gastrointestinal symptoms.

The link between gut and joint inflammation in IBD is currently unknown. However, two major theories explain the development of arthritis in IBD patients. First is the presence of gut bacteria and the second is the migration of gut lymphocytes to the joints [20].

While the specific causes of most types of SpAs are unknown, people who have a gene known as HLA-B27 are at a higher risk of developing AS, IBD associated arthritis, PsA, and reactive arthritis. However, not everyone expressing this gene will develop the disease. The patien in this study did not carry the HLA-B27 gene. Several non-HLA genes have also been identified in SpAs pathogenesis. Males have a higher risk of developing SpAs compared to females. In addition to genetic factors, environmental factors such as bacterial infections, stress, and microtrauma can also increase the risk of SpAs.

Several cytokines have been shown to participate in the inflammatory process of the SpAs. One of these cytokines is TNF alpha. Macrophages and macrophage-driven cytokines such as TNF-alpha and IL10 are mediators of disease inflammation. A few anti-TNF alpha therapies (infliximab, etanercept, adalimumab, golimumab, and certolizumab) have resulted in partial or full remission of symptoms in many patients. Treatment with TNF alpha inhibitors (human monoclonal antibodies also called biologics) has been recommended for patients suffering from IBD arthropathy. However, many patients treated with TNF alpha inhibitors, can over time, develop antibodies against them and make their action ineffective [28,29].

That is in fact what happened to this patient after six months of therapy with TNF alpha inhibitor Adalimumab. As such, the patient was treated with JAK2 inhibitor [30]. Janus kinase family of enzymes include JAK1, JAK2, JAK3, and TYK2. They are cytoplasmic tyrosine kinases associated with membrane cytokine receptors that mediate signaling of multiple cytokines and growth factors, contributing to the pathogenesis of multiple autoimmune disorders [31]. Therefore, JAK inhibitors are immune modulating medications, which inhibit the activity of one or more of the Janus kinase family of enzymes by interfering with the Janus Kinase/Signal Transducer and Activator of Transcription (JAK-STAT) signaling pathway in the lymphocytes [31]. They are used in the treatment of inflammatory diseases, rheumatoid arthritis, cancer and multiple skin conditions such as psoriatic arthritis. Patients treated with JAK inhibitors (called synthetic disease modifying drugs) do not develop antibodies against them as they are not monoclonal antibodies. They are targeted therapies, which act at a molecular level.

Partial response of the patient to TNF-alpha and almost full response to JAK2 inhibitor therapies is a strong indication that many of her clinical manifestations have an underlying immunological origin. The patient has widespread inflammation with systemic features that overlap specific rheumatic diseases. However, her exact rheumatic disease can't be definitively classified. Over a quarter of patients suffering from rheumatic disease having systemic symptoms can't be easily diagnosed. Diagnosing and treating rheumatic

diseases is one of the biggest challenges for many providers, including primary care physicians and specialists. Many patients can never be appropriately diagnosed, even years after the disease becomes symptomatic.

Here, a few theoretical immunological diagnoses for this patient are presented. The first theory is that this patient could be suffering from IBD arthropathy, which is a subtype of seronegative SpA. This theory is based on her history of UC, and many rheumatological symptoms such as joint disease.

Another theory is that this patient could be suffering from an USRD [23] or an Overlapped Syndrome [24]. If patients have features characteristic of an autoimmune disease such as Raynaud's phenomenon, arthralgias, myalgias or a positive ANA but do not meet criteria for a defined autoimmune disease they can be diagnosed as USRD. Other patients who meet criteria for two or more defined autoimmune conditions can be diagnosed by overlap syndrome. These patients suffer from an immunological disorder that overlaps many of the known auto inflammatory disorders such as Lupus, rheumatoid arthritis, mixed connective tissue disease, Behcet's Disease (BD), IBD arthropathy or seronegative SpA.

The patient in this case had early Raynaud phenomena. Her polyarthritis was presented with diffuse or migratory arthralgia, symmetrical or asymmetrical polyarthritis or oligoarthritis, migratory polyarthritis, prolonged morning stiffness, elevated erythrocyte sedimentation rate, positive ANA, and a dramatic response to anti-inflammatory therapy. Although this pattern suggests Rheumatoid Arthritis (RA), it does not fulfil the current criteria for diagnosing RA and it could be classified under USRD or overlap Syndrome.

Another possible classification of this patient's diagnosis could be under a subset of BD [32]. BD is a relatively uncommon chronic auto inflammatory disorder seen in patients of Eastern Asia to the Mediterranean (the ancient Silk Road) descent. It is a relapsing; multisystemic/multiorgan disorder characterized by mucocutaneous, ocular, vascular and central nervous system manifestations. Its clinical spectrum includes oral and genital ulcerations, uveitis, vascular, neurological, articular, renal and gastrointestinal manifestations. While the etiopathogenesis of the disease is unknown, genetic predisposition, environmental factors and immunological abnormalities have been implicated [32-34].

While HLA-B51 and HLA-B5 are important genetic factors in determining BD in clinical phenotypes, there are not useful markers for the diagnosis of BD. Therefore, diagnosis of BD is mostly based on symptoms. The patient in our study was negative for both HLA-B5 and HLA-B51. The patient in this report was born in the middle east and had GI, renal and mucocutaneous manifestations; oral and genital ulceration; eye inflammation; neurological involvement (dizziness, vertigo and neuropathy) and non-erosive, asymmetric, non-deforming arthritis. Many of these manifestations substantially subsided once the patient underwent the Upadacitinib or JAK 2 inhibitor therapy. In addition, the patient's IC, GERD, intolerability toward many foods and maldigestion were also among symptoms that subsided with the immunomodulator. Furthermore, the patient's thyroid and kidney functions all improved. And since she has been on Rinvoq, the patient's left ear's hearing loss no longer extend beyond the initial 30% (which occurred before the start of therapy). This brings up an important point about diagnosing patient with vestibular migraine, PPPD, fibromyalgia or anxiety without ruling out the presence of a rheumatological/autoimmune disease. Another interesting future study would be to see the effect of immunomodulator therapy on patients suffering from endometriosis and IC.

Conclusion

Many Immunological/Rheumatoid diseases are manifested in multiple organs. It is essential to have a comprehensive assessment and investigation of possible autoimmune diseases as a cause of complex medical manifestations rather than focusing on one organ. Common diagnosis such as vestibular migraines, PPPD, bacterial overgrowth, fibromyalgia, and anxiey need better evaluation to rule out the possibility of autoimmune disease. In any suspected case of undifferentiated rheumatoid disease or overlapped syndrome, treatment with an immunomodulatory agent is preferred to bilological agents and can largely help the patient's quality of life.

Acknowledgements

None.

Conflict of Interest

None.

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How to cite this article: Ayati, Mehrdad and Arezou Azarani. "Atypical Neurological and Gastrointestinal of Undifferentiated Systemic Rheumatic Disease/Overlap Syndrome Responded to JAK2 Inhibitor." *J Clin Case Rep* 14 (2024): 1588.