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CONTENIDO

Enero - Marzo 2018

High Intensity Interval Training (HIIT): What is it and how it can benefit our patients

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Resumen

Un estilo de vida sedentario se relaciona a una mayor incidencia de enfermedades cardiovasculares y endocrinas. Se ha demostrado que la actividad física proporciona adaptaciones fisiológicas que disminuyen la incidencia de enfermedades. La falta de tiempo ha sido identificada como uno de los obstáculos más comunes para ser físicamente activo. El entrenamiento en Intervalos de Alta Intensidad (HIIT, por sus siglas en inglés) se desarrolló como una estrategia de ejercicio eficiente en tiempo. Consiste en intervalos de esfuerzos "casi máximos" a una intensidad que provoca aproximadamente el 80% al 90% de la frecuencia cardíaca máxima seguida por períodos de recuperación. Estudios revelan que HIIT es una estrategia efectiva para aumentar el consumo máximo de oxígeno (VO2max) y la salud en general. Por lo tanto, las investigaciones disponibles indican que HIIT puede ser una estrategia segura, divertida y eficiente para promover la actividad física y la salud general en diferentes poblaciones.

Summary

A sedentary lifestyle has been linked to an increased incidence of cardiovascular and endocrinologic diseases, while physical activity has been shown to provide physiological adaptations that reduce incidence of these diseases. Lack of time has been identified as one of the common obstacles to be physically active. High Intensity Interval Training (HIIT) was developed as a time-efficient alternative. HIIT consists of intervals of 'near maximal' effort performed at an intensity that elicits about 80% to 90% of maximal heart rate separated by periods of recovery. Studies reveal that HIIT increases VO2max and cell mitochondrial content. These benefits provide better oxygen metabolism and improve overall health. Available research indicates that HIIT may be a safe and time-efficient strategy to promote physical activity and overall health in different populations.

I. PHYSICAL ACTIVITY: A KEY FOR HEALTH

Low physical activity has been linked to high morbidity and mortality rates in the general population.[1] Studies have shown that sedentary lifestyles increase the risk of developing diseases such as congestive heart failure, cerebrovascular accidents and diabetes mellitus. Lifestyle changes, including high physical activity, produce significant physiological and clinical benefits to overall health. [2]

The American College of Sports Medicine (ACSM) recommends a regimen consisting of at least 30 minutes of continuous moderate-intensity physical activity for 5 days per week or 25 minutes of continuous high-intensity physical activity for 3 days per week. Less than half of Americans meet this guidelines.[3] In order to improve overall health with physical activity, it is important to have a combination of stretching, aerobic, and strengthening exercises.

Endurance exercises have shown to improve aerobic metabolism, while resistance training increases muscle force-generating capacity.[4] Time availability is one of the main barriers to starting an exercise program.[3] Exercise programs such as interval training are designed to be time efficient and attractive to busy individuals.

II. DEFINITION OF HIGH INTENSITY INTERVAL TRAINING (HIIT):

Interval training is defined as intermittent periods of intense exercise separated by periods of recovery. [4,5] Modification of intensity and duration of work and recovery periods allows for the production of a nearly infinite number of interval training workout variations.[3] HIIT is the most popular interval training program. It consists of 'near maximal' efforts performed at an intensity that elicits about 80% to 90% of maximal heart rate (MHR), followed by a recovery period at 40% to 50% of MHR. [4] (Figure 1)

Two general regimens have been described: aerobic HIIT and resistance HIIT. Aerobic HIIT consists of using traditional aerobic exercise modalities such as running and cycling to improve cardiorespiratory fitness. Resistance HIIT uses body weight or resistance devices for high repetition resistance activities. [6] Some protocols use a combination of both regimens.

III. PHYSIOLOGICAL ADAPTATIONS:

The physiological adaptations after interval training are largely dependent on the intensity and duration of work intervals. The physiological benefits obtained by HIIT can be divided in three major categories: aerobic fitness, metabolic adaptations and vascular health.[6] These benefits may be secondary to the time spent near VO2max, higher muscle fiber recruitment and adaptations in cellular pathways. These adaptations include improved endothelial function, resting muscle glycogen content, muscle oxidative capacity and hydrogen ion buffering.[6]

HIIT improves aerobic metabolism by inducing peripheral and central adaptations. Peripheral adaptations include augmentation of skeletal muscle mitochondrial content and capillary density while central adaptations include increased maximal stroke volume and cardiac output.[3,6] HIIT can result in increased VO2max as early as 2–4 weeks after initiating training.[7,8] Recent studies suggest that HIIT protocols increase VO2max to a greater extent and faster than Moderate Intensity Continuous Training (MICT). [6,9]

HIIT also impacts metabolic health. It improves insulin sensitivity more effectively than MICT, especially in patients with high risk of Diabetes Mellitus type 2. The musculoskeletal system responds by increasing mitochondrial content by 25–35% after six to seven sessions of HIIT. This improves regulation of substrate metabolism by promoting a greater reliance on fat oxidation and creating a proportional decrease in carbohydrate oxidation. As a result, abdominal and total fat loss is significantly greater with HIIT when compared with MICT.[3] Regarding vascular health, HIIT exhibits improvement in endothelial function when compared to other forms of continuous exercise protocols.

HIIT also helps burn more calories after the workout is finished due to excess post-exercise oxygen consumption (EPOC).[10] EPOC is defined as a 2-hour period after an exercise routine where the body is restoring itself to pre-exercise levels, and thus using more energy. Caloric expenditure is about 6% to 15% greater with HIIT when compared to moderate continuous endurance training. HIIT seems to be a more efficient way to exercise and may be a good option for patients with multiple comorbidities.[4,11,12]

IV. PHYSICAL AND PSYCHOLOGICAL BENEFITS

The ability to easily adapt routines for all fitness level, pre-existing conditions and settings has made HIIT very popular in recent years. HIIT has been shown to be potentially beneficial for people suffering from cardiovascular diseases, cancer, diabetes mellitus, obesity and others. There is evidence that HIIT improves aerobic and anaerobic fitness, blood pressure,

cardiovascular health, insulin sensitivity, cholesterol profiles, abdominal fat, body weight, and muscle mass.[10] Also, sports performance has improved in different type of sports when HIIT regimens where implemented.[13,14,15]

Cardiovascular benefits of HIIT have been documented in patients with coronary artery disease (CAD), heart failure, stroke and hypertension.[16] Short bouts of interval training are useful in the initiation phase of cardiac rehabilitation. Moderate and/or longer-interval HIIT protocols appear more appropriate for the improvement and maintenance phases due to their high physiological demand.[17] HIIT is able to revert low VO2max, endothelial dysfunction, and inflammatory reactions more effectively than MICT in CAD patients.1 In summary, despite a considerably lower training volume and time commitment, HIIT may be superior, if not similar, to traditional MICT for managing and offsetting cardiovascular diseases.

Recent studies demonstrate the clinical benefit of exercise in cancer patients. Continuous aerobic exercise improves aerobic capacity, muscle strength, body composition, quality of life, cancer-related and fatigue. HIIT has similar results but in a shorter period of time, thus being a time-effective alternative.18 HIIT was found to be an effective and appropriate exercise strategy for obese patients. Benefits included weight loss and improved VO2max, resting heart rate, blood pressure and fasting blood glucose.[19,20]

HIIT increases sports performance parameters both in hockey and rugby players.[13,15] HIIT was also proven to increase maximal oxygen uptake, maximal pulmonary ventilation and stroke volume in cyclists when compared to endurance and sprint training.[14]

Regular physical activity has been shown to improve mental health and well-being. Physical activity is effective by reducing fatigue, improving affect and reducing symptoms of depression.[21] HIIT may be a viable time-efficient exercise strategy to target the psychological problems associated with physical inactivity. However, more studies are needed to compare it to traditional training strategies and to study benefits in specific groups suffering from mental health conditions.[22]

V. HOW TO CREATE A HIIT PROGRAM

Duration, intensity, and frequency of the work intervals and the length and intensity of the recovery intervals should be considered when designing a HIIT program. The high intensity work periods may range from 5 seconds to 8 minutes long.[10] The ratio of high intensity to recovery time intervals can vary depending on the subject's fitness level, ability to recover and the level of intensity.[10] Important elements to consider before starting a HIIT program include, a warm up period before workouts, awareness of subject's physical fitness and a realistic number of repetitions.[23]

Participants report higher enjoyment and adherence to HIIT routines when compared to MICT. HIIT could be an efficient method for encouraging adequate physical activity and overall health.[6,24] One ot the most popular HIIT programs is called "7 minute workout" which consists of aerobic, strengthening, and core stability exercises. The entire routine is comprised of 12 rounds of 30 second workouts followed by resting periods of 10 seconds in a 3:1 ratio. The seven minute workout uses a mix of exercise including planks, push-ups, lunges and other exercises to work different areas of the body.[25]

VI. SAFETY CONSIDERATIONS

ACSM recommends a base fitness level consisting of aerobic training 3 to 5 times a week for 20 to 60 min per session at a somewhat hard intensity for several weeks before starting HIIT training.[10] People who have comorbidities such as DMII, CAD and other should receive medical clearance before starting any type of exercise training including HIIT. A safe HIIT program should be tailored to meet the individual's optimal training capabilities.[10] In patients with heart disease, the risk of a cardiovascular event was found to be very low for both MICT and HIIT exercise programs. HIIT protocols are a safe and beneficial exercise program for cardiac patients.[26]

VII. FUTURE EVIDENCE

More studies are necessary to better understand how specific HIIT programs need to be adapted to specific comorbidities. Future studies should use standardized methods and outcome measures. Recently, other time efficient methods have been created, such as Sprint Interval Training (SIT). These new methods consist of "all out efforts" or maximal heart rate for a extremely short period of time. The evidence for SIT is growing promising similar results to HIIT with less work time.

VIII. CONCLUSION

High-intensity interval training (HIIT) is an effective and time-efficient method of improving cardiorespiratory and metabolic function. The ability to easily modify routines for all fitness level, pre-existing conditions and settings has made HIIT very popular. Research has shown similar or more benefits than continuous endurance training in less amount of time. HIIT programs lead to greater improvements in VO2max and other physiological adaptations when compared with continuous moderate-intensity training of equal volume and time commitment. Future studies may need to look for the best combination of

intensity, duration, frequency, and timing of work-to-rest intervals to identify and develop the most appropriate and complete routine for each population.

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Recurrent Pneumothorax in a woman with Endometriosis

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ABSTRACT

Catamenial pneumothorax is a rare cause of pneumothorax occurring in less than 5% of women with pelvic endometriosis. In this report, we present a 39-year-old woman who presented with a second episode of pneumothorax within a ten-year period of being diagnosed with endometriosis.

RESUMEN

Neumotórax catamenial es una causa rara de neumotórax que ocurre en menos de 5% de las mujeres con endometriosis pélvica. En este reporte, presentamos una mujer de 39 años que presentó un segundo episodio de neumotórax en un periodo de 10 años luego de haber sido diagnosticada con endometriosis.

Keywords

Catamenial pneumothorax (CP), spontaneous pneumothorax, endometriosis

INTRODUCTION

Spontaneous pneumothorax in a woman with history of endometriosis is known as catamenial pneumothorax (CP). A high index of suspicion is necessary to make the diagnosis and management is often delayed due to misdiagnosis. In this report, we present a young woman with endometriosis with two episodes of pneumothorax in a 12-year period.

CASE PRESENTATION

A 39-year-old woman presents to the emergency room with new onset chest pain and shortness of breath. Physical exam had decreased breath sounds on the right lung field. She referred onset of menstruation in the past 3 days despite the strict compliance with continuous noncyclical combination oral contraceptive pills (COCPs). Her past medical history included endometriosis, infertility, scoliosis, hypertension, and ruptured brain aneurysm which required neurosurgical intervention in October 2014. Genetic test for collagen disorders and alpha 1 antitrypsin were negative. She had an episode of right-sided pneumothorax attributed to a ruptured apical bleb 12 years prior, which was treated with pleurectomy via video-assisted thoracic surgery (VATS). Chest radiography (CXR) showed a right lung pneumothorax causing mass effect upon the mediastinal structures with left shift and a subtle right diaphragmatic perforation (Figure 1A). Tube thoracostomy resulted in partial re-expansion (30% persistent pneumothorax) of the right lung field and she continued to have persistent air leak for 7 days. Two chest CT scans were performed during this period which showed residual right-sided pneumothorax involving the right upper lung field with bibasilar atelectatic changes; no bullae or lesions suggestive of endometriosis were identified. Bronchoscopy showed clear patent airways with no significant findings. Due to the persistent pneumothorax, the patient was taken for open exploration (via right posterolateral thoracotomy) on day 8 of admission.

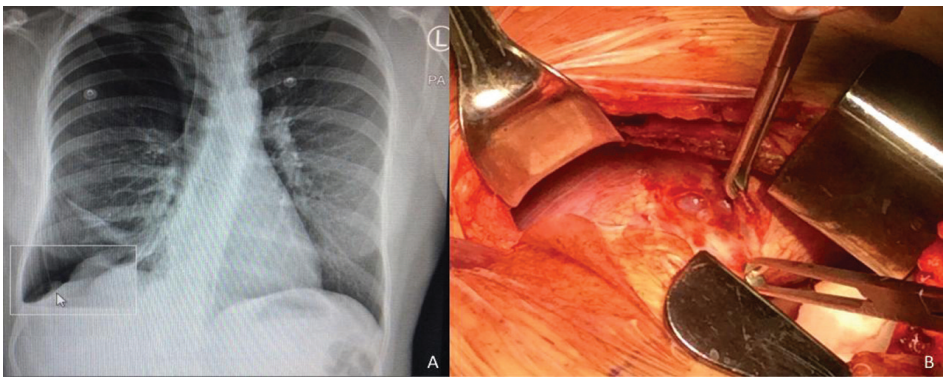

Figure 1. A. Chest X-ray. Right pneumothorax with perforation **at the right diaphragm (area magnified 2x). B. Diaphragmatic fenestrations.** Intra-operative findings of diaphragmatic fenestrations with liver protrusions.

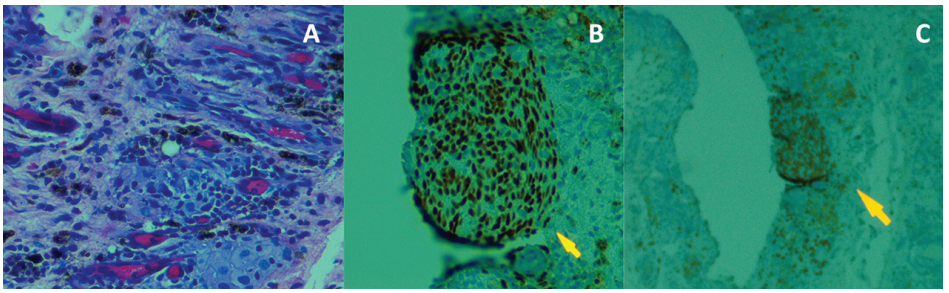

Figure 2. Microscopic Findings. A. H&E stain. Parietal pleura biopsy: pleural tissue with chronic inflammation, hemosiderin deposits, and focal mesothelial hyperplasia (40x). **B/C. Immunostaining (40x).** Estrogen and progesterone receptors positive, respectively.

On gross inspection no bullae, blebs, or endometriosis implants were identified. However, on inspection of the diaphragm, several 2-6 mm central tendon defects with protrusion of liver were identified (Figure 1B). The defects were repaired with simple plication with plegated 3-0 monofilament absorbable suture. Mechanical pleural abrasion with limited pleurectomy was also performed. Biopsies were taken from the right middle lobe and pleural cavity. Post-op day 1 imaging demonstrated she was free of pneumothorax, she no longer had air leak, and the chest tube was removed. The pathology report found that the biopsies stained positive for both estrogen and progesterone receptors supporting the diagnosis of catamenial pneumothorax (Figure 2). Prior to discharge she was placed on a combination of a pro-gestational and GnRH analogue therapies, with depot medroxyprogesterone acetate and leuprolide, respectively. At 1 year follow up she was free of symptoms and back to her normal daily activities.

DISCUSSION

CP classically presents within 72 hours before or after onset of menses in women with history of pelvic endometriosis1-3. Our patient developed CP despite strict adherence to COCPs which in most cases controls the progression of endometriosis. She had a pneumothorax 12 years prior which may have been related to her endometriosis however, this was not considered at that time. This could have been due to the young age of presentation which may have led physicians to wait for a second episode to establish a temporal relationship with menses. Her history of infertility could have been the determining risk factor which, along with a history of pelvic surgery, has been found to be the one of the strongest predictors of CP5. Few reports have documented CP in women on ovulatory suppression[2]. To our knowledge, this is the second case of CP reported in a Puerto Rican woman[7].

Characteristic lesions of CP include endometrial foci at the pleura, lungs, and/or diaphragm. Single or multiple diaphragm fenestrations at the central tendon have also been described1-2. However, CXR rarely reveals small diaphragmatic defects suggestive of perforation, as was demonstrated in our patient's CXR (Figure 1A and 1B). Interestingly, histological evidence of thoracic endometriosis (endometrial stroma and glands or stroma only plus positive staining for estrogen/progesterone receptor) is not revealed in all cases1. Rousset-Jablonski et al. found that histologically confirmed thoracic endometriosis occurs in 64 to 87% of surgical biopsies1-5.

Several theories have tried to explain the pathophysiology of CP. These theories include the anatomic model, the visceral model and the metastatic/lymphovascular micro-embolization theory. In this patient, the anatomic and/or visceral pleural models may account for both pneumothorax events as diaphragmatic fenestrae were found at the central tendon. A thorough examination of the diaphragm was not performed at her first intervention as they may have been present at that time.

Surgery and adjunct hormonal suppression constitute the treatment of choice for CP. Surgical approach includes videoassisted thoracic surgery (VATS), video-assisted

minithoracotomy, or open thoracotomy. We decided to explore via right thoracotomy for various reasons: 1) the recurrent nature of our patient's pneumothorax, which had been treated with VATS 12 years prior 2) pre-operative CT scans did not show a bleb or an obvious lesion as the etiology of the new recurrence, 3) persistent leak after 7 days of tube drainage, 4) right thoracotomy provided excellent visualization in a previous CP patient operated by the senior author [7]. The principles of operative management include: 1) resection of all visible intrathoracic lesions such as blebs, bullae, endometrial implants via limited wedged resection, 2) diaphragmatic plication with or without resection, 3) and mechanical or chemical pleurodesis.

Despite best efforts, CP reoccurs in 5% and 25% of surgically treated patients at 6 and 12 months, respectively[1,6,8]. Adjuvant gonadotropin-releasing hormone (GnRH) analogues reduce recurrence rate down to less than 5%[8]. Depot medroxyprogesterone acetate and leuprolide for 6 months after surgery prevents cyclical hormonal changes and induces suppression of ectopic endometrium until effective formation of pleural adhesions occur after pleurectomy. GnRH analogues are often chosen as first-line treatment due to their effectiveness at suppressing ovarian hormonal production but side effects (increased risk of osteoporosis, infertility, acute menopausal symptoms) could be a determining factor when choosing a hormonal agent. Even with combined treatment of surgery and hormonal suppression, up to 32% of women will experience recurrence[9].

In closing, we describe an unusual presentation of CP in a woman with severe endometriosis that had two episodes of pneumothorax within 12 years. Thoracic endome-triosis may have accounted for the first episode, but this was never confirmed.

High clinical suspicion for CP is important in any woman with history of endometriosis that presents with shortness of breath or pneumothorax. This will ensure proper surgical and medical management to address this complex clinical entity.

Conflict of Interest: The authors have declared that no conflict of interest exists.

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Upper Trunk Plexopathy due to Neck/Shoulder Traction after Xylazine Overdose

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Abstract Case of 38-year-old female with past medical history of intravenous drug abuse that came to our clinics with a chief compliant of left arm weakness and hyperalgesia. She had an overdose event with xylazine (a2-receptor partial agonist-sedative/tranquilizer), remaining on the bathtub floor with neck/shoulder traction around 2 to 3 hours. EMG and NCS showed an increased spontaneous activity, diminish recruitment and increase insertional activity on left brachioradialis, biceps, deltoid, infraspinatus and supraspinatus which suggested upper trunk plexopathy of the brachial plexus. Literature evidence showed that xylazine can present with CNS depression, cardiovascular effects, endocrine effects and respiratory depression, now we can include muscular effects to the general toxidrome such as, muscle relaxation which in this case the muscle of the neck and shoulder were so relaxed that no mechanism of protection was activated, and a traction injury took place with passive stretch developing a condition on the Brachial Plexus.

INTRODUCTION

Xylazine HCL is a a2-receptor partial agonist that works at the central nervous system as an anti-nociception, sedative and tranquilizer in the veterinary clinics. Also known as "anesthesia de caballo" (horse anesthetic) in the streets of Puerto Rico, which is popular among drug users (Reyes et al., 2012). In humans has properties of hypotension, respiratory depression, hyperglycemia, orthostatic hypotension and bradycardia secondary to vagal stimulation (Ruiz-ColOn, Chavez-Arias, Diaz-Alcala, & Martinez, 2014). Half-life of xylazine in human had been calculated once in Hoffman, U. 2001, which suggested a half-life of 4.5 hours in plasma, also its therapeutic index is so small that even small doses can gave the drug user an overdose, even death has been reported (Ruiz-Colon et al., 2012). Drug user reported that the combination of Xylazine with Heroin gave them even higher effect than heroin alone (Ruiz-ColOn et al., 2012). It has also been reported that one interviewee narrate that after xylazine and heroin abused, the subject fall to sleep for around 5 hours (Torruella, 2011).

We report a case of brachial plexus dysfunction due to neck/shoulder traction after xylazine overdose, which presented with sign and symptoms of upper trunk plexopathy, a complication of the drug abuse that was not observed in previous reports. Depending of the different divisions of brachial plexus involved, clinical presentation will vary, and is important to understand that moderate to severe traction injury may be presented the patient no opportunity of recovery. The brachial plexus gives sensory/motor innervation to upper extremities, it arise from C5 to Ti nerves roots and is located between lower neck and axilla (Lapegue, 2014). In other words, injury to the brachial plexus compromises the upper extremity sensation and motor function.

Indeed, the EDX study will help to differentiate the location of the lesion (nerve root vs cord vs trunk) and to determine the possible prognosis of the lesion or injury.

CASE REPORT

A 38-year-old female patient with past medical history of hypothyroidism and intravenous drug abuse, which comes (September/1/2016) to our clinic with chief complaint of left arm weakness and hyperalgesia. Patient refers he has been presenting with left arm numbness and weakness for the last 3 weeks after she had an overdose event with xylazine, remaining in the floor of bathroom with neck/shoulder traction around 2 to 3 hours. Patient refers numbness and weakness that has been improving since the day of the incident. She refers that when lying flat in supine

position she is able to mobilize better her left shoulder.

Patient is on multiple medications such as buprenorphine, Neurontin, Relafen and xylazine in the daily basis. Toxic habits, as referred by patient, included heroin, cocaine and anesthetics (xylazine- alpha 2 adrenergic agonist). Physical examination consistent with a subject alert, awake and oriented in person, place and time. Inspection suggested left deltoid, supraspinatus and infraspinatus atrophy, multiple tattoos, medial winging of left scapula, old sear of 3.2 cm length left side of neck. Also with left shoulder tenderness to palpation, decrease sensation to soft touch, deep tendon reflex of left bicep 0, left triceps +2 and left brachioradialis +1. Muscle manual test is consistent with left deltoid 2/5, biceps 3/5, triceps 3/5, wrist flexion and extension 5/5, and handgrip 5/5.

EMG & NCV FINDINGS

Evaluation of the left median, left ulnar, and the right ulnar nerves sensory conduction studies showed reduced amplitude of the SNAP (supplemental material). All remaining sensory and motor nerves (as indicated in the following tables) were within normal limits (latencies, amplitude, NCV).

Needle evaluation of the left Brachioradialis muscle showed increased insertional activity. The left Biceps muscle showed increased insertional activity, moderately increased spontaneous activity, and moderately decreased interference pattern. The left Supraspinatus muscle showed increase insertional activity, moderately increased spontaneous activity and diminished recruitment pattern. The left Deltoid and the left Infraspinatus muscles showed increased insertional activity, moderately increased spontaneous activity, diminished recruitment pattern, and moderately decreased interference pattern. All remaining muscles (as indicated in the following table) showed no evidence of electrical instability.

DISCUSSION

Brachial Plexopathy is a peripheral neuropathy that occurs due to direct damage to the brachial plexus. Lesions could be related to various mechanisms such as traction, compression, laceration, ischemia, radiation and stretch (Wilbotnn, 2007). To diagnose a specific trunk or cord disorder of the Brachial Plexus it requires an extensive electrodiagnostic study to differentiate the type and location of the lesion or injury. In our case, the patient presented with increased insertional and spontaneous activity, and diminished recruitment pattern in left Brachioradialis, left Biceps, left Supraspinatus, left Infraspinatus and left Deltoid, which are muscle innervated by neurons that cross through the upper trunk of the Brachial Plexus. Also physical exam, as explain before in the case summary, concur with EDX results.

These findings together lead the electrodiagnostic impression of an abnormal study, with electrophysiological evidence of a subacute left brachial plexus injury involving the upper trunk with axonal loss and ongoing denervation secondary to traction injury. Our patient presented with this condition due to the position of the head and neck on the ground that provoked a non-traumatic passive stretch on the Brachial Plexus which cause the nerve damage as a consequence of or secondary to an overdose of xylazine before lying down in the bathtub.

As previously stipulated, xylazine properties on human beings could promote hypotension, bradycardia, respiratory depression among other, but also works as a muscle relaxant and a sedative, which in this case the muscle of the neck and shoulder were so relaxed that no mechanism of protection was activated, and a traction injury took place with passive stretch developing a lesion on the left Brachial Plexus.

It is understood that a detailed clinical exam and electrodiagnostic test results can lead the physician to a proper determination of the affected area in the brachial plexus. There is no consensus of treatment to upper trunk Brachial Plexopathy but the treatment recommended in this patient included physical and occupational therapy to improve strength, decrease pain, maintain range of motion, and maximize independence. Intermittent use of sling was recommended for upper extremity support due to proximal weakness. Also, patient was advised of drug rehabilitation program to improve her quality of life and to be re-established in the society to continue a productive life. Finally, according to medical literature, xylazine presented with CNS depression, cardiovascular effects, endocrine effects and respiratory depression (Ruiz-Colon et al., 2014), but after this case presentation we can include the muscular effects, such a considerably muscle relaxation, to the general toxidrome, which could contribute to an additional complication such as focal neuropathic disorder.

Nerve Conduction Studies

Anti Sensory Summary Table

Site	NR	Peak (ms)	Norm Peak (ms)	0-P Amp (p.V)	Norm O-P Amp	Neg Area (07-ms)	Onset (ms)	Full Dur (ms)	Sitel	Site2	Delta - P (ms)	Dist (cm)	Vel (m/s)	Norm Vel (m/s)
Left Lat Ante Brach Cutan Anti Sensory (Lat Forearm)														
Lat Biceps		2.8		512		92.15	0.9	7.56	Lat Biceps	Lat Forearm	2.8	0.0		
Right Lat Ante Brach Cutan Anti Sensory (Lat Forearm)														
Lat Biceps		1.6		6.6		38.32	1.3	6.84	Lat Biceps	[Art Forearm	1.6	0.0		
Left Median Anti Sensory (2nd Digit)														
Wrist		3.5 7.24	<3.6	7g<..2<-4: i..		>10	2.6	2.56	Wrist	2nd Digit	3.5	14.0	40	>39
Right Median Anti Sensory (2nd Digit)														
Wrist		3.5	<3.6	20.8	>10	17.81	2.8	4.44	Wrist	2nd Digit	3.5	**14.0**	40	>39
Left Radial Anti Sensory (Base 1st Digit)														
Wrist		2.7	<3.1	7.7		4.76	**1.9**	3.38	Wrist	Base 1st Digit	2.7	OM		
Right Radial Anti Sensory (Base 1st Digit)														
Wrist		2.9	<3.1	14.1		10.79	2.2	2.41	Wrist	Base 1st Digit	2.9	0.0		
Left Ulnar Anti Sensory (5th Digit)														
Wrist -.		3.6	<3.7	.e . r' ⁄0 ,		>15.0	12.11	2.9	2.44	Wrist	5th Digit	3.6	14.0	39	>38
Right Ulnar Anti Sensory (5th Digit)														
Wrist		3.5	<3.7	p .!,	>15.0	7.87	2.9	3.09	Wrist	5th Digit	3.5	14.0	40	>38

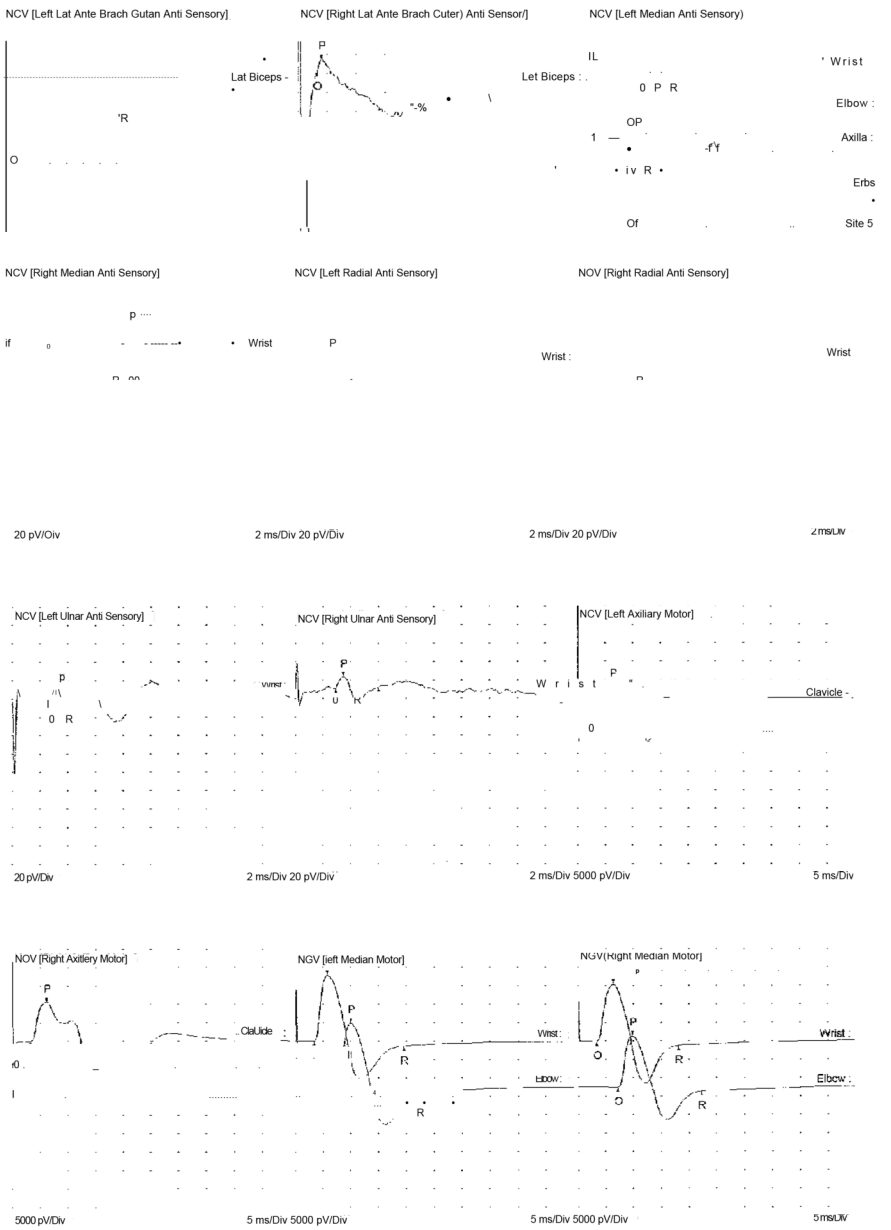
Motor Summary Table

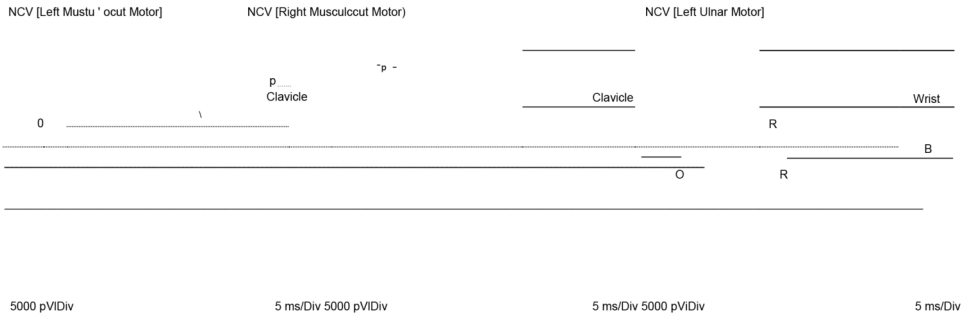
Site	NR	Onset (ms)	Norm Onset (ms)	0-P Amp (mV)	Norm 0-P Amp	Neg Area (mV•ms)	Full Dur (ms)	Sitel	Site2	Delta-0 (ms)	Dist (cm)	Vel (m/s)	Norm Vel
Left Axillary Motor (Deltoid)													
Clavicle		3.1	<5	3.2		7.70	13.20						
Right Axillary Motor (Deltoid)													
Clavicle		3.2	<5	10.9		55.98	16.80						
Left Median Motor (Abd Poll Brev)													
Wrist		3.4	<4.2	17.8	>5	64.94	16.25	Elbow	Wrist	3.9	24.5	63	>50
Elbow		7.3		17.4		64.09	15.39						
Right Median Motor (Abd Poll Brev)													
Wrist		3.4	<4.2	15.4	>5	57.87	14.69	Elbow	Wrist	3.8	23.5	62	>50
Elbow		7.2		14.0		49.75	15.08						
Left Musculocut Motor (Biceps)													
Clavicle		4.3	<5.7	3.0		7.89	11.41						
Right Musculoeut Motor (Biceps)													
Clavicle		4.5	<5.7	5.6		9.16	4.69						
Left Ulnar Motor (Abd Dig Minimi)													
Wrist		3.3	<4.2	8.7	>3	37.43	16.33	13 Elbow	Wrist	2.9	18.0	62	>53
B Elbow		6.2		8.4		37.95	16.80						
Right Ulnar Motor (Abd Dig Minimi)													
Wrist		3.2	<4.2	8.1	>3	39.27	16.09	B Elbow	Wrist	2.7	17.0	63	>53
B Elbow		5.9		8.0		39.39	14.69						

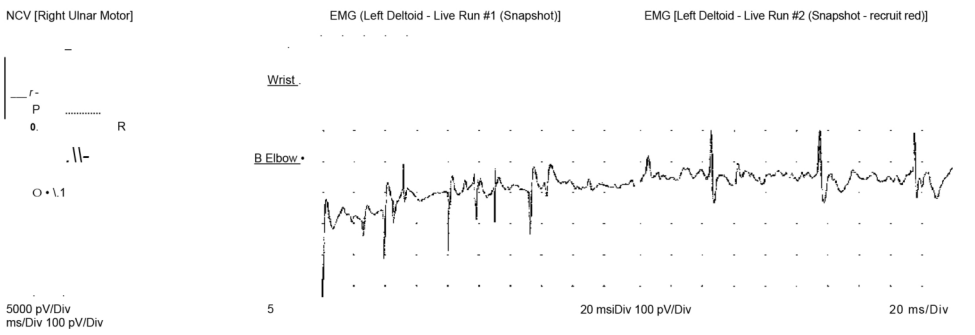
EMG

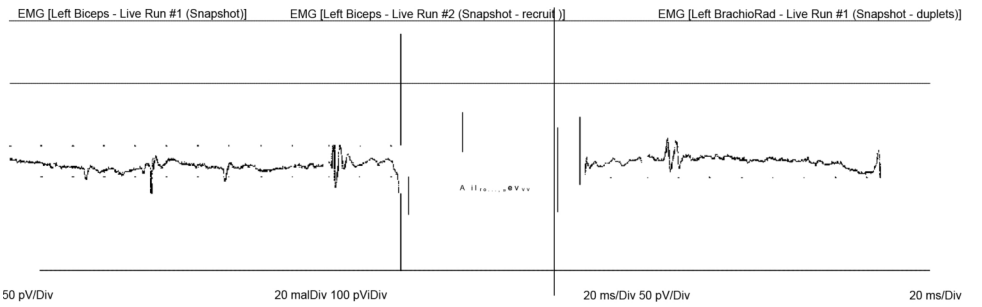
Side	Muscle	Nerve	Root	Ins Act	Fibs	Psw	Amp	Dur	Poly	Recrt	Int Pat	Comment
Left	ABD Dig MM	Ulnar	C8-T1	Nml	Nml	Mill	Nml	Nml	0	Nml	Nml	
Left	1stDorlrit	Ulnar	C8-T1	Nml	Nml	Nml	Nml	Nml	0	Nml	Nml	
Left	PronatorTeres	Median	C6-7	Nml	Nml	Nml	Nml	Nml	0	Nml	Nml	
Left	BrachioRad	Radial	C5-6	:'C..	Nml	Nml	Nml	Nml	0	Nml	Nml	
Left	Biceps	Musculocut	C5-6	t'			Nml	Nml	0	NmI	*sir*	
Left	Triceps	Radial	C6-7-8	Nml	Nml	Nml	Nml	Nml	0	Nml	Nml	
Left	Supraspinatus	SupraScap	C5-6	Nml	Nml	,..	Nml	Nml	0	Reduced	Nml	
Left	Deltoid	Axillary	C5-6	net			Null	Nml	0	Reduced *75%		
Left	Infraspinatus	SupraScap	C5-6				Nml	Nml	0	Reduced *75%		

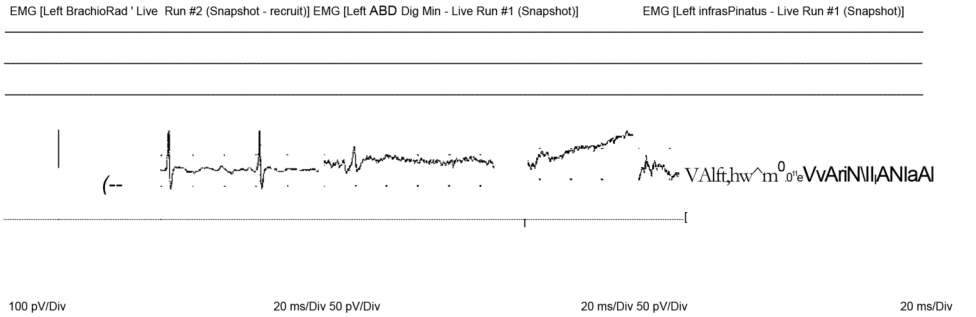
Waveforms:




NCV [Left Mustu ' ocut Motor]
NCV [Right Musculccut Motor)
NCV [Left Ulnar Motor]
Clavicle
Clavicle
Wrist
R
B
O
R
5000 pVIDiv
5 ms/Div 5000 pVIDiv
5 ms/Div 5000 pViDiv
5 ms/Div


NCV [Right Ulnar Motor]
EMG (Left Deltoid - Live Run #1 (Snapshot)]
EMG [Left Deltoid - Live Run #2 (Snapshot - recruit red)]
Wrist
B Elbow
5000 pV/Div
ms/Div 100 pV/Div
5
20 msiDiv 100 pV/Div
20 ms/Div


EMG [Left Biceps - Live Run #1 (Snapshot)]
EMG [Left Biceps - Live Run #2 (Snapshot - recruit)]
EMG [Left BrachioRad - Live Run #1 (Snapshot - duplets)]
50 pV/Div
20 malDiv 100 pViDiv
20 ms/Div 50 pV/Div
20 ms/Div


EMG [Left BrachioRad ' Live Run #2 (Snapshot - recruit)]
EMG [Left ABD Dig Min - Live Run #1 (Snapshot)]
EMG [Left infrasPinatus - Live Run #1 (Snapshot)]
100 pV/Div
20 ms/Div 50 pV/Div
20 ms/Div 50 pV/Div
20 ms/Div


EMG [Left Infraspinatus - Live Run 112 (Snapshot - recruit)]
100 pV/Div
20 ms/Div

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INDICATION

- XELJANZ (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).
- Limitations of Use: Use of XELJANZ in combination with biologic therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Avoid use of XELJANZ/XELJANZ XR in patients with an active, serious infection, including localized infections, or with chronic or recurrent infection.

In the UC population, XELJANZ 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily.

Opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients who were treated with XELJANZ 10 mg twice daily.

The risks and benefits of treatment with XELJANZ/XELJANZ XR should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection, or those who have lived or traveled in areas of endemic TB or mycoses. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infection.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy.

Malignancies (including solid cancers and lymphomas) were observed more often in patients treated with XELJANZ 10 mg twice daily dosing in the UC long-term extension study.

Other malignancies were observed in clinical studies and the post-marketing setting including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer. NMSCs

Please see additional Important Safety Information and brief summary of full Prescribing Information, including **BOXED WARNING**, on the following pages. For current full Prescribing Information, please visit XELJANZPI.com.

IMPORTANT SAFETY INFORMATION (cont'd)

MALIGNANCIES (cont'd)

have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. In the UC population, treatment with XELJANZ 10 mg twice daily was associated with greater risk of NMSC.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal perforations have been reported in XELJANZ clinical trials, although the role of JAK inhibition is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). There was no discernable difference in frequency of gastrointestinal perforation between the placebo and the XELJANZ arms in clinical trials of patients with UC, and many of them were receiving background corticosteroids. XELJANZ/XELJANZ XR should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs).

LABORATORY ABNORMALITIES

Lymphocyte Abnormalities: Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a count less than 500 cells/mm^3. In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm^3, treatment with XELJANZ/XELJANZ XR is not recommended. Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Monitor lymphocyte counts at baseline and every 3 months thereafter.

Neutropenia: Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3) compared to placebo. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with an ANC less than 1000 cells/mm^3. For patients who develop a persistent ANC of 500-1000 cells/mm^3, interrupt XELJANZ/XELJANZ XR dosing until ANC is greater than or equal to 1000 cells/mm^3. In patients who develop an ANC less than 500 cells/mm^3, treatment with XELJANZ/XELJANZ XR is not recommended. Monitor neutrophil counts at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Anemia: Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a hemoglobin level less than 9 g/dL. Treatment with XELJANZ/XELJANZ XR should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment. Monitor hemoglobin at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Liver Enzyme Elevations: Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. If drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until this diagnosis has been excluded. Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury.

Lipid Elevations: Treatment with XELJANZ was associated with dose-dependent increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. There were no clinically relevant changes in LDL/HDL cholesterol ratios. Manage patients with hyperlipidemia according to clinical guidelines. Assessment of lipid parameters should be performed approximately 4-8 weeks following initiation of XELJANZ/XELJANZ XR therapy.

VACCINATIONS

Avoid use of live vaccines concurrently with XELJANZ/XELJANZ XR. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ/XELJANZ XR therapy.

PATIENTS WITH GASTROINTESTINAL NARROWING

Caution should be used when administering XELJANZ XR to patients with pre-existing severe gastrointestinal narrowing. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs utilizing a non-deformable extended release formulation.

HEPATIC and RENAL IMPAIRMENT

Use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended.

For patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 5 mg twice daily, reduce to XELJANZ 5 mg once daily.

For UC patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 10 mg twice daily, reduce to XELJANZ 5 mg twice daily.

ADVERSE REACTIONS

The most common serious adverse reactions were serious infections. The most commonly reported adverse reactions during the first 3 months in controlled clinical trials in patients with rheumatoid arthritis (RA) with XELJANZ 5 mg twice daily and placebo , respectively, (occurring in greater than or equal to 2% of patients treated with XELJANZ with or without DMARDs) were upper respiratory tract infection, nasopharyngitis, diarrhea, headache, and hypertension. The safety profile observed in patients with active psoriatic arthritis treated with XELJANZ was consistent with the safety profile observed in RA patients.

Adverse reactions reported in ≥5% of patients treated with either 5 mg or 10 mg twice daily of XELJANZ and ≥1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials for ulcerative colitis were: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

USE IN PREGNANCY

Available data with XELJANZ/XELJANZ XR use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis and UC in pregnancy. In animal studies, tofacitinib at 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings. The relevance of these findings to women of childbearing potential is uncertain. Consider pregnancy planning and prevention for females of reproductive potential.

Please see additional Important Safety Information on the previous page and brief summary of full Prescribing Information, including **BOXED WARNING**, on the following pages. For current full Prescribing Information, please visit XELJANZPI.com.

References: 1. Data on file. Pfizer Inc, New York, NY. **2.** XELJANZ [prescribing information]. New York, NY: Pfizer Inc; May 2018.

XELJANZ® (tofacitinib)/XELJANZ® XR (tofacitinib)

BRIEF SUMMARY OF PRESCRIBING INFORMATION. SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with XELJANZ/XELJANZ XR should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

INDICATIONS AND USAGE

Rheumatoid Arthritis

XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Psoriatic Arthritis

XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease modifying antirheumatic drugs (DMARDs).

- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ulcerative Colitis

XELJANZ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

- Limitations of Use: Use of XELJANZ in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infection, and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids.

In the UC population, XELJANZ treatment with 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily. Additionally, opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients who were treated with XELJANZ 10 mg twice daily.

Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

Avoid use of XELJANZ/XELJANZ XR in patients with an active, serious infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating XELJANZ/XELJANZ XR in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR. XELJANZ/XELJANZ XR should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ/XELJANZ XR should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infections.

Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Discontinuation and monitoring criteria for lymphopenia are recommended.

Tuberculosis Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of XELJANZ/XELJANZ XR.

Anti-tuberculosis therapy should also be considered prior to administration of XELJANZ/XELJANZ XR in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering XELJANZ/XELJANZ XR.

Viral Reactivation Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with XELJANZ. The impact of XELJANZ/XELJANZ XR on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ/XELJANZ XR. The risk of herpes zoster is increased in patients treated with XELJANZ/XELJANZ XR and appears to be higher in patients treated with XELJANZ in Japan and Korea.

Malignancy and Lymphoproliferative Disorders Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy. Malignancies were observed in clinical studies of XELJANZ.

In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving XELJANZ

with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with XELJANZ.

During the 2 PsA controlled clinical studies there were 3 malignancies (excluding NMSC) in 474 patients receiving XELJANZ plus nonbiologic DMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients in the placebo plus nonbiologic DMARD group (3 months exposure) and 0 malignancies in 106 patients in the adalimumab plus nonbiologic DMARD group (12 months exposure). No lymphomas were reported. Malignancies have also been observed in the long-term extension study in psoriatic arthritis patients treated with XELJANZ.

During the UC controlled clinical studies (8-week induction and 52-week maintenance studies), which included 1220 patients, 0 cases of solid cancer or lymphoma were observed in XELJANZ-treated patients. In the long-term extension study, malignancies (including solid cancers and lymphomas) were observed more often in patients treated with XELJANZ 10 mg twice daily.

In Phase 2B, controlled dose-ranging trials in *de-novo* renal transplant patients, all of whom received induction therapy with basiliximab, high-dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with XELJANZ (2.3%) compared to 0 out of 111 patients treated with cyclosporine.

Other malignancies were observed in clinical studies and the post-marketing setting, including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.

Non-Melanoma Skin Cancer Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. In the UC population, treatment with XELJANZ 10 mg twice daily was associated with greater risk of NMSC.

Gastrointestinal Perforations Events of gastrointestinal perforation have been reported in clinical studies with XELJANZ, although the role of JAK inhibition in these events is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).

There was no discernable difference in frequency of gastrointestinal perforation between the placebo and the XELJANZ arms in clinical trials of patients with UC, and many of them were receiving background corticosteroids.

XELJANZ/XELJANZ XR should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections
- Malignancy and Lymphoproliferative Disorders
- Gastrointestinal Perforations
- Laboratory Abnormalities

Clinical Trials Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Rheumatoid Arthritis The clinical studies described in the following sections were conducted using XELJANZ. Although other doses of XELJANZ have been studied, the recommended dose of XELJANZ is 5 mg twice daily.

The recommended dose for XELJANZ XR is 11 mg once daily.

The following data includes two Phase 2 and five Phase 3 double-blind, controlled, multicenter trials. In these trials, patients were randomized to doses of XELJANZ 5 mg twice daily (292 patients) and 10 mg twice daily (306 patients) monotherapy, XELJANZ 5 mg twice daily (1044 patients) and 10 mg twice daily (1043 patients) in combination with DMARDs (including methotrexate) and placebo (809 patients). All seven protocols included provisions for patients taking placebo to receive treatment with XELJANZ at Month 3 or Month 6 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Therefore, some analyses that follow include patients who changed treatment by design or by patient response from placebo to XELJANZ in both the placebo and XELJANZ group of a given interval. Comparisons between placebo and XELJANZ were based on the first 3 months of exposure, and comparisons between XELJANZ 5 mg twice daily and XELJANZ 10 mg twice daily were based on the first 12 months of exposure.

The long-term safety population includes all patients who participated in a double-blind, controlled trial (including earlier development phase studies) and then participated in one of two long-term safety studies. The design of the long-term safety studies allowed for modification of XELJANZ doses according to clinical judgment. This limits the interpretation of the long-term safety data with respect to dose.

The most common serious adverse reactions were serious infections.

The proportion of patients who discontinued treatment due to any adverse reaction during the 0 to 3 months exposure in the double-blind, placebo-controlled trials was 4% for patients taking XELJANZ and 3% for placebo-treated patients.

Overall Infections In the seven controlled trials, during the 0 to 3 months exposure, the overall frequency of infections was 20% and 22% in the 5 mg twice daily and 10 mg twice daily groups, respectively, and 18% in the placebo group.

The most commonly reported infections with XELJANZ were upper respiratory tract infections, nasopharyngitis, and urinary tract infections (4%, 3%, and 2% of patients, respectively).

Serious Infections In the seven controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.5 events per 100 patient-years) who received placebo and 11 patients (1.7 events per 100 patient-years) who received XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 1.1 (-0.4, 2.5) events per 100 patient-years for the combined 5 mg twice daily and 10 mg twice daily XELJANZ group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, serious infections were reported in 34 patients (2.7 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 33 patients (2.7 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was -0.1 (-1.3, 1.2) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The most common serious infections included pneumonia, cellulitis, herpes zoster, and urinary tract infection.

Tuberculosis In the seven controlled trials, during the 0 to 3 months exposure, tuberculosis was not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven controlled trials, during the 0 to 12 months exposure, tuberculosis was reported in 0 patients who received 5 mg twice daily of XELJANZ and 6 patients (0.5 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.5 (0.1, 0.9) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

Cases of disseminated tuberculosis were also reported. The median XELJANZ exposure prior to diagnosis of tuberculosis was 10 months (range from 152 to 960 days).

Opportunistic Infections (excluding tuberculosis) In the seven controlled trials, during the 0 to 3 months exposure, opportunistic infections were not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven controlled trials, during the 0 to 12 months exposure, opportunistic infections were reported in 4 patients (0.3 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 4 patients (0.3 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0 (-0.5, 0.5) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The median XELJANZ exposure prior to diagnosis of an opportunistic infection was 8 months (range from 41 to 698 days).

Malignancy In the seven controlled trials, during the 0 to 3 months exposure, malignancies

excluding NMSC were reported in 0 patients who received placebo and 2 patients (0.3 events per 100 patient years) who received either XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 0.3 (-0.1, 0.7) events per 100 patient- years for the combined 5 mg and 10 mg twice daily XELJANZ group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, malignancies excluding NMSC were reported in 5 patients (0.4 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 7 patients (0.6 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.2 (-0.4, 0.7) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ. One of these malignancies was a case of lymphoma that occurred during the 0 to 12 month period in a patient treated with XELJANZ 10 mg twice daily.

The most common types of malignancy, including malignancies observed during the long-term extension, were lung and breast cancer, followed by gastric, colorectal, renal cell, prostate cancer, lymphoma, and malignant melanoma.

Laboratory Abnormalities

Lymphopenia In the controlled clinical trials, confirmed decreases in absolute lymphocyte counts below 500 cells/mm^3 occurred in 0.04% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

Confirmed lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections.

Neutropenia In the controlled clinical trials, confirmed decreases in ANC below 1000 cells/mm^3 occurred in 0.07% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

There were no confirmed decreases in ANC below 500 cells/mm^3 observed in any treatment group.

There was no clear relationship between neutropenia and the occurrence of serious infections.

In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical trials.

Liver Enzyme Elevations Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were observed in patients treated with XELJANZ. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of XELJANZ, or reduction in XELJANZ dose, resulted in decrease or normalization of liver enzymes.

In the controlled monotherapy trials (0-3 months), no differences in the incidence of ALT or AST elevations were observed between the placebo, and XELJANZ 5 mg, and 10 mg twice daily groups.

In the controlled background DMARD trials (0-3 months), ALT elevations greater than 3x ULN were observed in 1.0%, 1.3% and 1.2% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. In these trials, AST elevations greater than 3x ULN were observed in 0.6%, 0.5% and 0.4% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively.

One case of drug-induced liver injury was reported in a patient treated with XELJANZ 10 mg twice daily for approximately 2.5 months. The patient developed symptomatic elevations of AST and ALT greater than 3x ULN and bilirubin elevations greater than 2x ULN, which required hospitalizations and a liver biopsy.

Lipid Elevations In the controlled clinical trials, dose-related elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were observed at one month of exposure and remained stable thereafter. Changes in lipid parameters during the first 3 months of exposure in the controlled clinical trials are summarized below:

- Mean LDL cholesterol increased by 15% in the XELJANZ 5 mg twice daily arm and 19% in the XELJANZ 10 mg twice daily arm.
- Mean HDL cholesterol increased by 10% in the XELJANZ 5 mg twice daily arm and 12% in the XELJANZ 10 mg twice daily arm.
- Mean LDL/HDL ratios were essentially unchanged in XELJANZ-treated patients.

In a controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy.

In the long-term safety population, elevations in lipid parameters remained consistent with what was seen in the controlled clinical trials.

Serum Creatinine Elevations In the controlled clinical trials, dose-related elevations in serum creatinine were observed with XELJANZ treatment. The mean increase in serum creatinine was <0.1 mg/dL in the 12-month pooled safety analysis; however with increasing duration of exposure in the long-term extensions, up to 2% of patients were discontinued from XELJANZ treatment due to the protocol-specified discontinuation criterion of an increase in creatinine by more than 50% of baseline. The clinical significance of the observed serum creatinine elevations is unknown.

Other Adverse Reactions Adverse reactions occurring in 2% or more of patients on 5 mg twice daily or 10 mg twice daily XELJANZ and at least 1% greater than that observed in patients on placebo with or without DMARD are summarized in the table below.

Common Adverse Reactions* in Clinical Trials of XELJANZ for the Treatment of Rheumatoid Arthritis With or Without Concomitant DMARDs (0-3 Months)

Preferred Team	XELJANZ 5 mg Twice Daily N = 1336 (%)	XELJANZ 10 mg Twice Daily** N = 1349 (%)	Placebo N = 809 (%)
Upper respiratory tract infection	4	4	3
Nasopharyngitis	4	3	3
Diarrhea	4	3	2
Headache	4	3	2
Hypertension	2	2	1

N reflects randomized and treated patients from the seven clinical trials.

* reported in ≥2% of patients treated with either dose of XELJANZ and ≥1% greater than that reported for placebo.

** the recommended dose of XELJANZ for the treatment of rheumatoid arthritis is 5 mg twice daily.

Other adverse reactions occurring in controlled and open-label extension studies included:

Blood and lymphatic system disorders: Anemia

Infections and infestations: Diverticulitis

Metabolism and nutrition disorders: Dehydration

Psychiatric disorders: Insomnia

Nervous system disorders: Paresthesia

Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, sinus congestion, interstitial lung disease (cases were limited to patients with rheumatoid arthritis and some were fatal)

Gastrointestinal disorders: Abdominal pain, dyspepsia, vomiting, gastritis, nausea

Hepatobiliary disorders: Hepatic steatosis

Skin and subcutaneous tissue disorders: Rash, erythema, pruritus

Musculoskeletal, connective tissue and bone disorders: Musculoskeletal pain, arthralgia, tendonitis, joint swelling

Neoplasms benign, malignant and unspecified (including cysts and polyps): Non-melanoma skin cancers

General disorders and administration site conditions: Pyrexia, fatigue, peripheral edema

Clinical Experience in Methotrexate-Naïve Patients Study RA-VI was an active-controlled clinical trial in methotrexate-naïve patients. The safety experience in these patients was consistent with Studies RA-I through V.

Psoriatic Arthritis XELJANZ 5 mg twice daily and 10 mg twice daily were studied in 2 double-blind Phase 3 clinical trials in patients with active psoriatic arthritis (PsA).

Study PsA-I (NCT01877668) had a duration of 12 months and enrolled patients who had an inadequate response to a nonbiologic DMARD and who were naïve to treatment with a TNF blocker. Study PsA-I included a 3-month placebo-controlled period and also included adalimumab 40 mg subcutaneously once every 2 weeks for 12 months.

Study PsA-II (NCT01882439) had a duration of 6 months and enrolled patients who had an inadequate response to at least one approved TNF blocker. This clinical trial included a 3-month placebo controlled period.

In these combined Phase 3 clinical trials, 238 patients were randomized and treated with XELJANZ 5 mg twice daily and 236 patients were randomized and treated with XELJANZ 10 mg twice daily. All patients in the clinical trials were required to receive treatment with a stable dose of a nonbiologic DMARD [the majority (79%) received methotrexate]. The study population randomized and treated with XELJANZ (474 patients) included 45 (9.5%) patients aged 65 years or older and 66 (13.9%) patients with diabetes at baseline.

The safety profile observed in patients with active psoriatic arthritis treated with XELJANZ was consistent with the safety profile observed in rheumatoid arthritis patients.

Ulcerative Colitis XELJANZ has been studied in patients with moderately to severely active UC in 4 randomized, double-blind, placebo-controlled trials (UC-I, UC-II, UC-III, and dose ranging UC-V) and an open-label long term extension study (UC-IV).

Adverse reactions reported in ≥5% of patients treated with either 5 mg or 10 mg twice daily of XELJANZ and ≥1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials were: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

Induction Trials (Study UC-I, UC-II, and UC-V):
Common adverse reactions reported in ≥2% of patients treated with XELJANZ 10 mg twice daily and ≥1% greater than that reported in patients receiving placebo in the 3 induction trials were: headache, nasopharyngitis, elevated cholesterol levels, acne, increased blood creatine phosphokinase, and pyrexia.

Maintenance Trial (Study UC-III)
Common adverse reactions reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported in patients receiving placebo are shown in the table below.

Common Adverse Reactions* in UC Patients during the Maintenance Trial (Study UC-III)

Preferred Term	XELJANZ 5 mg Twice Daily N = 198 (%)	XELJANZ 10 mg Twice Daily N = 196 (%)	Placebo N = 198 (%)
Nasopharyngitis	10	14	6
Elevated cholesterol levels**	5	9	1
Headache	9	3	6
Upper respiratory tract infection	7	6	4
Increased blood creatine phosphokinase	3	7	2
Rash	3	6	4
Diarrhea	2	5	3
Herpes zoster	1	5	1
Gastroenteritis	3	4	3
Anemia	4	2	2
Nausea	1	4	3

* reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported for placebo.

** includes hypercholesterolemia, hyperlipidemia, blood cholesterol increased, dyslipidemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal, or lipids increased.

In the long-term extension study, malignancies (including solid cancers, lymphomas and NMSC) were observed more often in patients treated with XELJANZ 10 mg twice daily. Four cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one fatality in a patient with advanced cancer.

Dose-dependent adverse reactions seen in patients treated with XELJANZ 10 mg twice daily, in comparison to 5 mg twice daily, include the following: herpes zoster infections, serious infections, and NMSC.

DRUG INTERACTIONS

The table below includes drugs with clinically important drug interactions when administered concomitantly with XELJANZ/XELJANZ XR and instructions for preventing or managing them.

Clinical Relevant Interactions Affecting XELJANZ and XELJANZ XR When Coadministered with Other Drugs

Strong CP3A4 Inhibitors (e.g., ketoconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ/ XELJANZ XR is recommended
Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ/ XELJANZ XR is recommended
Strong CYP3A4 Inducers (e.g., rifampin)	
Clinical Impact	Decreased exposure to tofacitinib and may result in loss of or reduced clinical response
Intervention	Coadministration with XELJANZ/ XELJANZ XR is not recommended
Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine)	
Clinical Impact	Risk of added immunosuppression; coadministration with biologic DMARDs or potent immunosuppressants has not been studied in patients with rheumatoid arthritis, psoriatic arthritis, or UC.
Intervention	Coadministration with XELJANZ/ XELJANZ XR is not recommended

USE IN SPECIFIC POPULATIONS

All information provided in this section is applicable to XELJANZ and XELJANZ XR as they contain the same active ingredient (tofacitinib).

Pregnancy

Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to XELJANZ/XELJANZ XR during pregnancy. Patients should be encouraged to enroll in the XELJANZ/XELJANZ XR pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call the toll free number 1-877-311-8972.

Risk Summary Available data with XELJANZ/ XELJANZ XR use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis and UC in pregnancy *(see Clinical Considerations)*. In animal reproduction studies, fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 73-times and 6.3-times the maximum recommended dose of 10 mg twice daily, respectively. Further, in a peri and post-natal study in rats, tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73-times the recommended dose of 5 mg twice daily and approximately 36 times the maximum recommended dose of 10 mg twice daily, respectively *(see Data)*.

The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risks in the U.S. general population of major birth defects and miscarriages are 2 to 4% and 15 to 20% of clinically recognized pregnancies, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/ Fetal Risk
Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data
Animal Data In a rat embryofetal developmental study, in which pregnant rats received tofacitinib during organogenesis, tofacitinib was teratogenic at exposure levels approximately 146 times the recommended dose of 5 mg twice daily, and approximately 73 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 100 mg/kg/day in rats). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively; and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). In addition, there was an increase in post-implantation loss, consisting of early and late resorptions, resulting in a reduced number of viable fetuses. Mean fetal body weight was reduced. No developmental toxicity was observed in rats at exposure levels approximately 58 times the recommended dose of 5 mg twice daily, and approximately 29 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in pregnant rats).

In a rabbit embryofetal developmental study in which pregnant rabbits received tofacitinib during the period of organogenesis, tofacitinib was teratogenic at exposure levels approximately 13 times the recommended dose of 5 mg twice daily, and approximately 6.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in rabbits) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail defects. In addition, there was an increase in post-implantation loss associated with late resorptions. No developmental toxicity was observed in rabbits at exposure levels approximately 3 times the recommended dose of 5 mg twice daily, and approximately 1.5 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in pregnant rabbits).

In a peri- and postnatal development study in pregnant rats that received tofacitinib from gestation day 6 through day 20 of lactation, there were reductions in live litter size, postnatal

survival, and pup body weights at exposure levels approximately 73 times the recommended dose of 5 mg twice daily, and approximately 36 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 50 mg/kg/day in rats). There was no effect on behavioral and learning assessments, sexual maturation or the ability of the F1 generation rats to mate and produce viable F2 generation fetuses in rats at exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in rats).

Lactation

Risk Summary There are no data on the presence of tofacitinib in human milk, the effects on a breastfed infant, or the effects on milk production. Tofacitinib is present in the milk of lactating rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adults treated with XELJANZ/XELJANZ XR, such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 18 hours after the last dose of XELJANZ or 36 hours after the last dose of XELJANZ XR (approximately 6 elimination half-lives).

Data
Following administration of tofacitinib to lactating rats, concentrations of tofacitinib in milk over time paralleled those in serum, and were approximately 2 times higher in milk relative to maternal serum at all time points measured.

Females and Males of Reproductive Potential

Contraception
Females In an animal reproduction study, tofacitinib at AUC multiples of 13 times the recommended dose of 5 mg twice daily and 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings. However, there is uncertainty as to how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential.

Infertility
Females Based on findings in rats, treatment with XELJANZ/XELJANZ XR may result in reduced fertility in females of reproductive potential. It is not known if this effect is reversible.

Pediatric Use
The safety and effectiveness of XELJANZ/XELJANZ XR in pediatric patients have not been established.

Geriatric Use
Of the 3315 patients who enrolled in rheumatoid arthritis Studies I to V, a total of 505 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. The frequency of serious infection among XELJANZ-treated subjects 65 years of age and older was higher than among those under the age of 65.

Of the 1156 XELJANZ treated patients in the UC program, a total of 77 patients (7%) were 65 years of age or older. The number of patients aged 65 years and older was not sufficient to determine whether they responded differently from younger patients.

As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Use in Diabetics
As there is a higher incidence of infection in diabetic population in general, caution should be used when treating patients with diabetes.

Renal Impairment
Moderate and Severe Impairment
XELJANZ-treated patients with moderate or severe renal impairment had greater tofacitinib blood concentrations than XELJANZ-treated patients with normal renal function. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate or severe renal impairment.

- Rheumatoid arthritis and psoriatic arthritis patients with moderate or severe renal impairment receiving XELJANZ XR should switch to XELJANZ and adjust the dosage.

Mild impairment
No dosage adjustment is required in patients with mild renal impairment.

Hepatic Impairment
Severe Impairment
XELJANZ/XELJANZ XR has not been studied in patients with severe hepatic impairment; therefore, use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended.

Moderate Impairment
XELJANZ-treated patients with moderate hepatic impairment had greater tofacitinib blood concentration than XELJANZ-treated patients with normal hepatic function. Higher blood concentrations may increase the risk of some adverse reactions. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate hepatic impairment.

- Rheumatoid arthritis and psoriatic arthritis patients receiving XELJANZ XR should switch to XELJANZ and adjust the dosage.

Mild Impairment
No dosage adjustment of XELJANZ/XELJANZ XR is required in patients with mild hepatic impairment.

Hepatitis B or C Serology
The safety and efficacy of XELJANZ/XELJANZ XR have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

OVERDOSAGE
There is no specific antidote for overdose with XELJANZ/XELJANZ XR. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions.

This brief summary is based on XELJANZ®/XELJANZ® XR (tofacitinib) Prescribing Information LAB-0445-13.0

Issued: May 2018

Secondary Adrenal Insufficiency due to Chronic Opioid Therapy

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A 47-year-old male, active smoker with history of esophageal carcinoma, who visited the emergency room (ER) complaining of dizziness, weakness and fatigue. He denied fever, chills, nausea, vomiting, chest pain, or shortness of breath. Vital signs revealed blood pressure of 85/50 mmHg (MAP, 62 mmHg), heart rate of 89 bpm, temperature 98.5˚F and peripheral saturation of 100% at room air. Physical examination did not show hyperpigmentation of his scar, oral mucosa or hands. Initial laboratory results were remarkable for glucose of 58 mg/dL.

After initial evaluation, intravenous resuscitation with one liter of 0.9% NaCl at 250mL/hr was promptly started, without resolution of hypotension. Dextrose 25g was also administered for hypoglycemia, with a follow up capillary blood glucose increased to 191 mg/dL. Due to persistent hypoglycemia and hypotension, patient was admitted to the Internal Medicine ward. Further workup including Insulin, beta hydroxybutyrate, C-peptide and Somatomedin C levels were performed, with all results within reference range. PPD and HIV were negative. Abdominal CT was negative for metastatic disease or adrenal hemorrhage. However, AM cortisol was low at 2.42 µg/dL and ACTH was inappropriately low at 6 pg/mL, consistent with Secondary Adrenal Insufficiency.

Upon medication review, patient had been prescribed a Fentanyl patch of 100mcg/hr for chronic pain management. Opioids, such as Fentanyl, are known to induce Secondary Adrenal Insufficiency. After clinical stabilization patient was discharged with Hydrocortisone 15mg in the morning and 10mg in the afternoon.

DISCUSSION:

Currently with Opioid Crisis, our goal is to raise concerns about a possible lethal, but easily treatable adverse effect of chronic opioid therapy, if not timely recognized, Secondary Adrenal Insufficiency.

Mariela Navarro-Torres, MD
Janet Colón-Castellano, MD
Francis P. Baco, MD

Aggressive type of Tumor in an Atypical Anatomical area

Adrián Castañeda Hidalgo, MD[1], L. León Pons, MD[1], N.M. Pérez Crespo, MD[1], J.W. Perdomo Medrano, MD[1], F.J. Díaz Lozada, MD[1]
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INTRODUCTION

Mucosal melanoma is an exceptionally rare and aggressive condition comprising approximately 1 % of all melanomas. Anorectal mucosal melanoma account for about 0.05% of all colorectal malignancies. Due to the nature of the disease presenting initially with general symptoms and anatomical lesions not commonly visible to patients, the early evaluation and diagnosis is usually complex. Has also been noticed that at the initial presentation of this condition, it already presents with spread metastasis and lymphadenopathies.

CASE REPORT

An 83-year-old female presented to her family physician with symptoms of constipation, anal pressure and weight loss of 16 pounds for one-year period. The initial laboratory workup revealed a positive fecal occult blood test. For that reason, a further workup was done including: endorectal ultrasound, colonoscopy and biopsy. Pathology reported and diagnosed by immunohistochemistry markers of S-100 positive and HMB45 positive, revealing results which are compatible with melanoma. To evaluate for metastasis, CT scan and PET scan were performed, remarkable for multiple hyper metabolic lesions involving rectum, liver and lungs, along with pelvic and inguinal lymphadenopathies corresponding to a metastatic process.

This case was discussed in the Multidisciplinary Board of our institution to evaluate for treatment options, and systemic therapy was recommended. On follow up oncology evaluation, treatment options were discussed with patient who agreed with Pembrolizumab as monotherapy, which is used globally for unresectable or metastatic melanoma. A brain MRI was also performed to rule out metastasis. Additional workup of genetic screening is currently in process, since a possible hereditary cancer syndrome could be considered in this patient, due to the fact that she has first line family members with history of colorectal and gastric cancer.

DISCUSSION

We present for your consideration this exceptional case presenting with advanced stage cancer, without previous screening colonoscopy that could have helped with early detection and eradication of the Melanoma. This case highlights the progressive nature of this type of Melanoma, which besides not being very common, carries a poor prognosis. This presentation also creates awareness about this disease and encourages physicians to inquire more about the possibilities of early diagnosis, trying to advice patients about the importance of screening colonoscopy after the age of 50. Also, with a family history of colorectal cancer, genetic testing might be beneficial providing useful information regarding treatment options.

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Aldicarb, an unusual toxic agent with a highly effective treatment

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INTRODUCTION

Aldicarb is a carbamate insecticide commonly used in Puerto Rico and the Caribbean. It can be found in the insecticide commonly known as "Tres Pasitos", and is the most potent carbamate insecticide on the market.

CASE REPORT

This is the case of a 56- year-old male patient with history of recurrent major depressive disorder and two past suicide attempts who arrived via ambulance to the emergency room (ER). He was found by his wife and daughters lying in the bathroom floor with foamy secretions around his mouth, vomit of gastric content, urinary and fecal incontinence. No pills were identified in the surroundings, but the patient's family members heard him say "Tres Pasitos" repeatedly.

On physical examination at ER triage area, patient had a Glasgow Coma Scale of 6, was not following commands or verbalizing; had loss of sphincter control and, bilateral miosis. He looked pale, diaphoretic, tachypneic, with increased lacrimation and salivation; also had cold extremities to palpation. Initial vital signs were: Temperature 96.5^{0}F, Pulse 98 bpm, Respiratory Rate 31/minute, Blood Pressure 182/96 mmHg, and peripheral O2 saturation 90% at room air.

At the ER, peripheral oxygen saturation decreased to 54% at room air; therefore, the patient was endotracheally intubated. Basic metabolic panel and arterial blood gases suggested high anion gap metabolic acidosis with respiratory alkalosis. Patient was admitted to the medical intensive care unit; Atropine and Pralidoxime chloride were promptly administered. Two days after admission, patient underwent successful extubation and was transferred to the Internal Medicine ward. After clinically stable, he was transferred to the Psychiatric Intensive Care Unit and discharged 4 days after admission.

DISCUSSION

This case is an excellent example of the importance of adequate history taking skills for an accurate and early diagnosis. It also highlights how the adequate management improves patient's prognosis and decreases mortality. Since the diagnosis of Aldicarb toxicity was made promptly, adequate therapy with Atropine and Pralidoxime was provided soon after arrival to the ER with an excellent response to medical therapy.

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Carlos Pérez, MD
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Helicobacter Pylori associated Immune Thrombocytopenia

Dora Eiko Mitsue Watanabe Ballarta, MD[1]
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INTRODUCTION

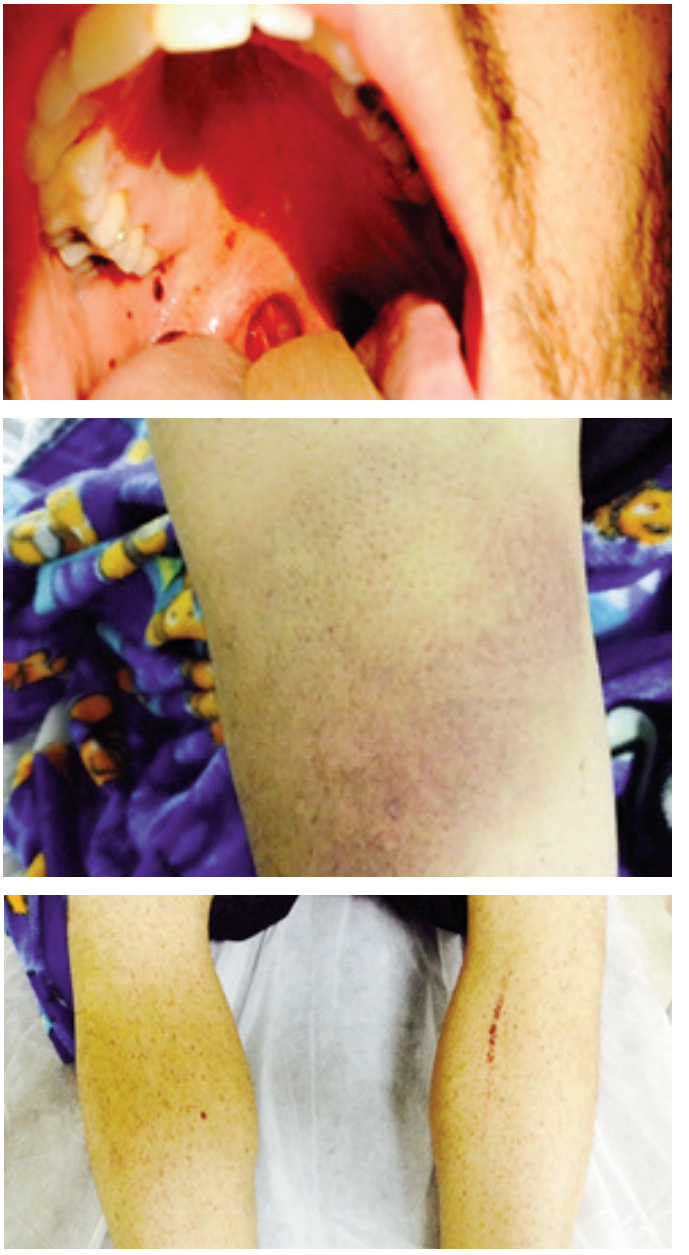
Idiopathic Thrombocytopenic Purpura (ITP) is a common hematologic disorder characterized by platelet autoantibodies, low platelet counts, and bleeding. The development of Helicobacter pylori (H. pylori) associated Idiopathic thrombocytopenic purpura appears to depend on multiple factors. Approximately 25 million Americans suffer from H.Pylori disease at some point in their lifetime. Each year there are 500,000 to 850,000 new cases and the incidence of immune thrombocytopenia among adults in the USA is estimated to be 3.3 per 100,000 adults/year. Eradication therapy is simple and inexpensive, the advantage of avoiding long-term immunosuppressive treatment for those who respond. The statistics about H. Pylori associated with immune thrombocytopenia is not clear yet. This is a case of a previously healthy man with multiple bruises and gum bleeding, whom after discarding other possible causes, the association with H.Pylori was considered.

CASE REPORT

A 35-year-old previously healthy man with a history of chronic right knee pain who was complaining of many bruises, multiple petechial lesions on his mucosa and skin, including palms and soles, who then presented with gum bleeding for the past 3 months. He is an active smoker and marijuana user. Family history was noncontributory. On physical exam, vitals were stable. Labs results reported 4,000/mL platelets, HIV: nonreactive, Hepatitis panel: nonreactive, ANA: negative, CMV: negative, EBV: negative, CRP: negative 0.10, H. Pylori: positive of 2.79. After treatment with Rituximab, platelet levels and lesions improved slightly, but after patient received treatment for H. Pylori, labs revealed marked improvement of platelet levels.

DISCUSSION

ITP is a diagnosis of exclusion that needs to be considered



Presented with many bruises, multiple petechial lesions on his mucosa and skin, and with gum bleeding for the past 3 months.

in patients with thrombocytopenia and associated H. pylori. This association has been increasing in importance with more cases found in medical literature, showing that adequate treatment improves symptoms and platelet levels. This case raises concern about the importance of keeping in mind the association between thrombocytopenia and H. Pylori infection.

LEARNING POINTS

I. Awareness and recognition of H. pylori infection as an etiology of ITP. II. Early treatment of H. pylori infection could increase platelet count by a decrease in antibody formation. III. Eradication of H. pylori infection has been variably associated with an increased platelet count in patients with ITP that depends on the severity of presenting thrombocytopenia. IV. Greater understanding and research of this presentation can lead to the development of effective methods of detection, pharmacotherapy, and use of available resources to treat ITP.

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Dora Eiko Mitsue Watanabe Ballarta, MD

Insidious Case of Late Onset Sarcoidosis in an Asymptomatic Male

Ariana González-Meléndez, MD; MPH, Nydia Burgos-Ortega MD; Lisannette Ramírez-Ramírez, MD

CASE REPORT

A 58-year-old male with history of hypertension, migraine and chronic back pain with radiculopathy sustained after trauma on active duty. Presented with abnormal findings of T12 and S2 suspicious for metastatic process after a follow-up MRI for his chronic back pain condition. Chest CT remarkable for multiple patchy opacities and spiculated micro-nodularities localized on right upper and medial lobe, and superior segment of the right lower lobe. Pet scan remarkable for multiple hypermetabolic lesions involving right lung, mediastinal lymph nodes and bone marrow. Infectious, inflammatory vs. metastatic condition were the differential diagnosis at that moment.

Pulmonary evaluation was performed, including various bronchoscopies which yielded no evidence of infectious process, nor granulomatous disease. Biopsy from right upper lobe was negative for malignancy. As lung biopsy did not disclose malignancy, it was decided to perform a second right upper lobe nodule biopsy which resulted remarkable for noncaseating granuloma without neoplastic changes nor infectious process. However, malignancy was still high in the differential. For that reason, oncology service recommended a vertebral biopsy from T12, where detached fragments from squamous carcinoma were reported. In view that bone biopsy findings did not correlate with lung biopsy findings, it was decided to monitor patient. After extensive workup, negative for infection, no evidence of pulmonary malignancy and evidence of noncaseating granuloma, sarcoidosis stage II was diagnosed, and patient started on oral steroids.

DISCUSSION

This case illustrates the potential for a late onset case of sarcoidosis in a 58-year-old male, who initially did not present with the pathological hallmark of caseating granuloma, nor manifestations consistent with sarcoidosis, such as uveitis, skin lesions, or x-ray findings. It has been studied that sarcoidosis presents different characteristics in elderly people in comparison to younger adults, including asymptomatic imaging abnormalities. Also, it has been studied that this condition poses a great impact in health care burden including psychosocial, economic, and comorbid conditions associated with this disease. Patients can experience a great burden of fatigue, depression, treatment side effects, and pain syndromes that may contribute to poor outcomes. Awareness of such condition is important, since misdiagnosis could lead to treatment delay and disease progression.

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Nydia Burgos-Ortega MD
Lisannette Ramírez-Ramírez, MD

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Urinary tract Schistosoma Haematobium infection in a Korean War Puerto Rican Veteran

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Summary An 87-year-old man was evaluated in the Infectious Diseases clinics due to evidence upon urine cytology sample consistent with Schistosoma haematobium ova. Routine urinalysis showed evidence of chronic microscopic hematuria due to which urine cytology samples were requested. The patient is a United States Army Veteran who participated in the Korean War where he was exposed to river water. He denied gross hematuria. Serum Schistosoma antibody serology was negative. Such assay used in our center has 96% sensitivity to S. mansoni, the endemic species in our region; however, it has low sensitivity to other Schistosoma species. A subsequent urinalysis post treatment with Praziquantel revealed resolution of microscopic hematuria. We present a case of urinary tract Schistosoma haematobium infection in a patient with chronic hematuria and significant, remote traveling history to an uncommonly endemic area.

Resumen Hombre de 87 años fue evaluado en las Clínicas de Infecciosas debido a una citología de orina que reveló evidencia de un huevo producido por Schistosoma haematobium. Un urinálisis de rutina había revelado hematuria microscópica, por lo cual se ordenó la citología de orina. El paciente es un Veterano militar de los Estados Unidos que participó en la Guerra de Corea donde estuvo expuesto a agua de río. La serología de Schistosoma fue negativa. La prueba utilizada en nuestra institución tiene alta sensitividad a S. mansoni, la especie endémica en nuestra región. Ésta tiene poca sensitividad para otras especies de Schistosoma. Luego del tratamiento con Praziquantel se realizó un urinálisis el cual reveló resolución de la hematuria microscópica. Presentamos un caso de infección del tracto urinario por Schistosoma haematobium en un paciente con hematuria microscópica acompañado por un historial de viaje a una región no comúnmente endémica.

INTRODUCTION

Schistosomiasis is an acute and chronic parasitic disease caused by trematodes, or commonly known as blood flukes, of the genus Schistosoma. Such parasitic infection is being successfully controlled in many countries but remains a major public health problem, with an estimated 200 million people infected, mostly in Africa [(1)]. It is caused by several species of the genus Schistosoma, of which S. mansoni, S. japonicum, S. mekongi, and S. haematobium are of public health importance [(4)]. Urinary schistosomiasis, caused by Schistosoma haematobium, is reported to be endemic in 54 countries in Africa and the Middle East [(7)]. Furthermore, less commonly associated to East Asian countries. Rather, Schistosoma japonicum is found in China, Taiwan, the Philippines, and Southeast Asia. Schistosoma mekongi is geographically distributed in concentrated regions of Laos and Cambodia. Schistosoma mansoni, japonicum and mekongi can cause intestinal schistosomiasis.

In the lifecycle of Schistosoma sp eggs are excreted on urine or feces of infected human then hatch in fresh water transforming into miracidium. The miracidium penetrates into the intermediate host a snail and multiplies asexually, then in 4-6 weeks cercariae emerges from the snail into the freshwater. Snails of the genera Biomphalaria and Bulinus act as intermediate hosts for Schistosoma mansoni and S. haematobium, respectively, primarily in the African continent [(6)]. Human infection occurs when the cercariae penetrates the skin. In approximately 6 weeks mature worms descend through venous circulation until its final habitat. It is considered that populations in close proximity to infested water bodies are at risk of schistosomiasis [(9)].

Acute schistosomiasis occurs 2-12 weeks after first heavy exposure to larvae and occurs during maturation and egg deposition known as Katayama Fever. It presents as an acute febrile illness with serum sickness like features with chills, fatigue, headache, myalgias, abdominal pain, and diarrhea. Adult S. hematobium worms live, mate and feed on blood in the vesical plexus. Eggs can appear in urine and feces of an infected human after 4-6 weeks. Large granulomas and fibrosis causes pathologic lesions in chronic schistosomiasis and can cause obstruction of urine flow through ureters and bladder in the case of S. haematobium. Identification of Schistosoma ova in the

affected tissue (s) is considered diagnostic; however, there are several serological tests that also aid in diagnostics. Within the several testing modalities, indirect immunofluorescence assay using S. mansoni adult worm sections has demonstrated high sensitivity in proven infections and areas of high and moderate endemicity; however, low sensitivity in non-endemic [5]. Also, a microsomal fraction of adult worms of S. mansoni has a high sensitivity and specificity for the detection of antibodies against S. mansoni in proven infections by ELISA [8]. Reactivity is much lower against heterologous sera from patients infected with S. haematobium, S. japonicum, or S. mekongi [10].

Chronic Schistosomiasis can cause different conditions; when the urinary system is infected there is a higher risk for bladder cancer, and when gastrointestinal tract and liver are infected, there is enlargement of the liver with abdominal distension. Eggs of S. haematobium are usually excreted through the urinary tract. Typical signs of urogenital schistosomiasis are macro- and microhematuria, proteinuria and pyuria [3]. The eggs of Schistosoma haematobium are large (110-170 µm long by 40-70 µm wide) and bear a conspicuous terminal spine. Eggs contain a mature miracidium when shed in urine. The ova of S. haematobium have characteristic "terminal spines" as demonstrated Figure 1, which is the identified pathology in the patient's urine cytology specimen (A Papanicolau smear staining technique was used).

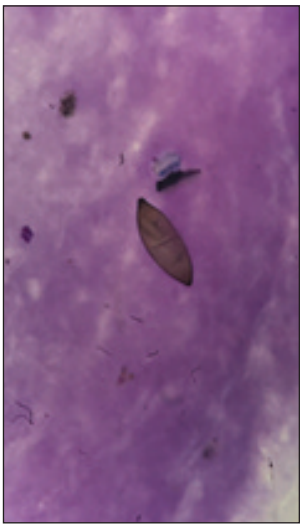

Figure 1
The ova of S. haematobium have characteristic "terminal spines" as demonstrated Figure 1, which is the identified pathology in the patient's urine cytology specimen. A Papanicolau smear staining technique was used.

The drug of choice for the treatment of schistosomiasis is Praziquantel. It acts against all schistosome species and has a good safety profile [2]. Treatment is to eradicate the infection and then manage the complications. However, the complications cannot be reversed, and patients can develop chronic illness (e.g. bladder carcinoma). It is unlikely that fibrosis already established can regress to any significant degree, but treatment of infection is important to prevent progression.

CASE REPORT

An 87-year-old male with a history of Type 2 diabetes mellitus and coronary artery disease was consulted to our service in the outpatient setting due to evidence upon urine cytology sample consistent with Schistosoma haematobium ova. Patient denied gross hematuria nor any other urinary symptoms. Routine urinalysis showed evidence of chronic microscopic hematuria due to which urine cytology samples were requested. Urine cytology did not reveal evidence of malignancy. Patient's risk factor for exposure to Schistosoma haematobium is having been stationed in Korea during the Korean War era, as patient is a United States Army veteran. He reported having used river water for drinking as well as having walked through rivers. He did report recalling a fever episode while in Korea that lasted approximately three to four days; however, does not recall if a diagnosis had been made at the time. He denied having visited any other neighboring countries such as Japan or other Asian countries.

Praziquantel, being the drug of choice to treat all infections due to Schistosoma sp, the patient was treated with a dose of Praziquantel 60mg/kg provided orally and dose divided into intervals of every eight hours in one day. No associated adverse effects were reported by the patient. Serum Schistosoma sp antibody serology was requested as well as Strongyloides sp antibody serology prior to treatment. Both serologies were negative. A subsequent urinalysis post treatment revealed resolution of microscopic hematuria.

This patient reported a febrile illness while in Korea which could have been attributed to Katayama Fever in the setting of acute schistosomiasis after recent exposure. The serological test used to assess for presence of Schistosoma sp antibodies IgG serology in our center uses the microsomal fraction of adult S. mansoni worms as antigen and is thus highly specific (99%) and sensitive (96%) for detection of infection caused by Schistosoma mansoni, which is endemic in our region. Although the assay is also specific for infections caused by other Schistosoma species (S. japonicum, S. haematobium, S.mekongi), its sensitivity

for these infections is lower. Therefore, this negative serology result can be explained by the low sensitivity of this test for Schistosoma haematobium and it further supports that exposure occurred while during stay in Asian continent (e.g. Korea), where he participated in active military duty.

DISCUSSION

We present a case of urinary tract Schistosoma haematobium infection in a patient with chronic hematuria and significant, remote traveling history to an uncommonly endemic area. Interestingly, this patient is a Korean War U.S. Veteran that reportedly had only been exposed to river waters in Korea, as he denied having been stationed in other adjacent countries in the Far East nor in Africa, where such parasite is considered endemic. To explain this, it is possible that globalization has expanded the range of Schistosoma species and their intermediate freshwater snail hosts. This has resulted in the occurrence of schistosomiasis in previously nonendemic regions. Our case aids in exemplifying the significantly wide range of infectious etiologies in patients with a traveling history.

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DISCUSSION

This case illustrates the potential for a late onset case of sarcoidosis in a 58-year-old male, who initially did not present with the pathological hallmark of caseating granuloma, nor manifestations consistent with sarcoidosis, such as uveitis, skin lesions, or x-ray findings. It has been studied that sarcoidosis presents different characteristics in elderly people in comparison to younger adults, including asymptomatic imaging abnormalities. Also, it has been studied that this condition poses a great impact in health care burden including psychosocial, economic, and comorbid conditions associated with this disease. Patients can experience a great burden of fatigue, depression, treatment side effects, and pain syndromes that may contribute to poor outcomes. Awareness of such condition is important, since misdiagnosis could lead to treatment delay and disease progression.

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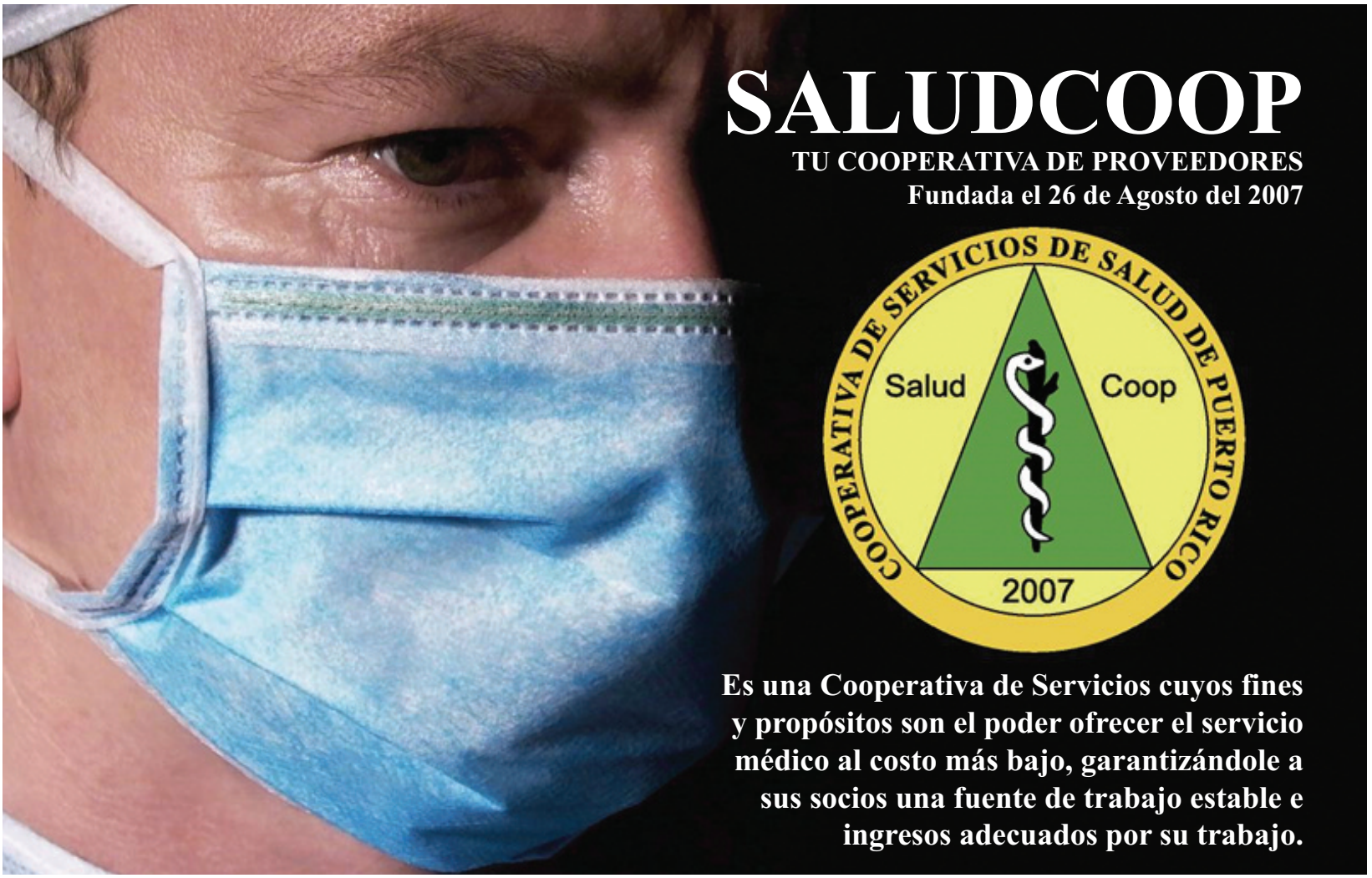

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TU COOPERATIVA DE PROVEEDORES
Fundada el 26 de Agosto del 2007

Es una Cooperativa de Servicios cuyos fines y propósitos son el poder ofrecer el servicio médico al costo más bajo, garantizándole a sus socios una fuente de trabajo estable e ingresos adecuados por su trabajo.

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5. Mostrar interés genuino en los fines y propósitos de la Cooperativa y sus proyectos.
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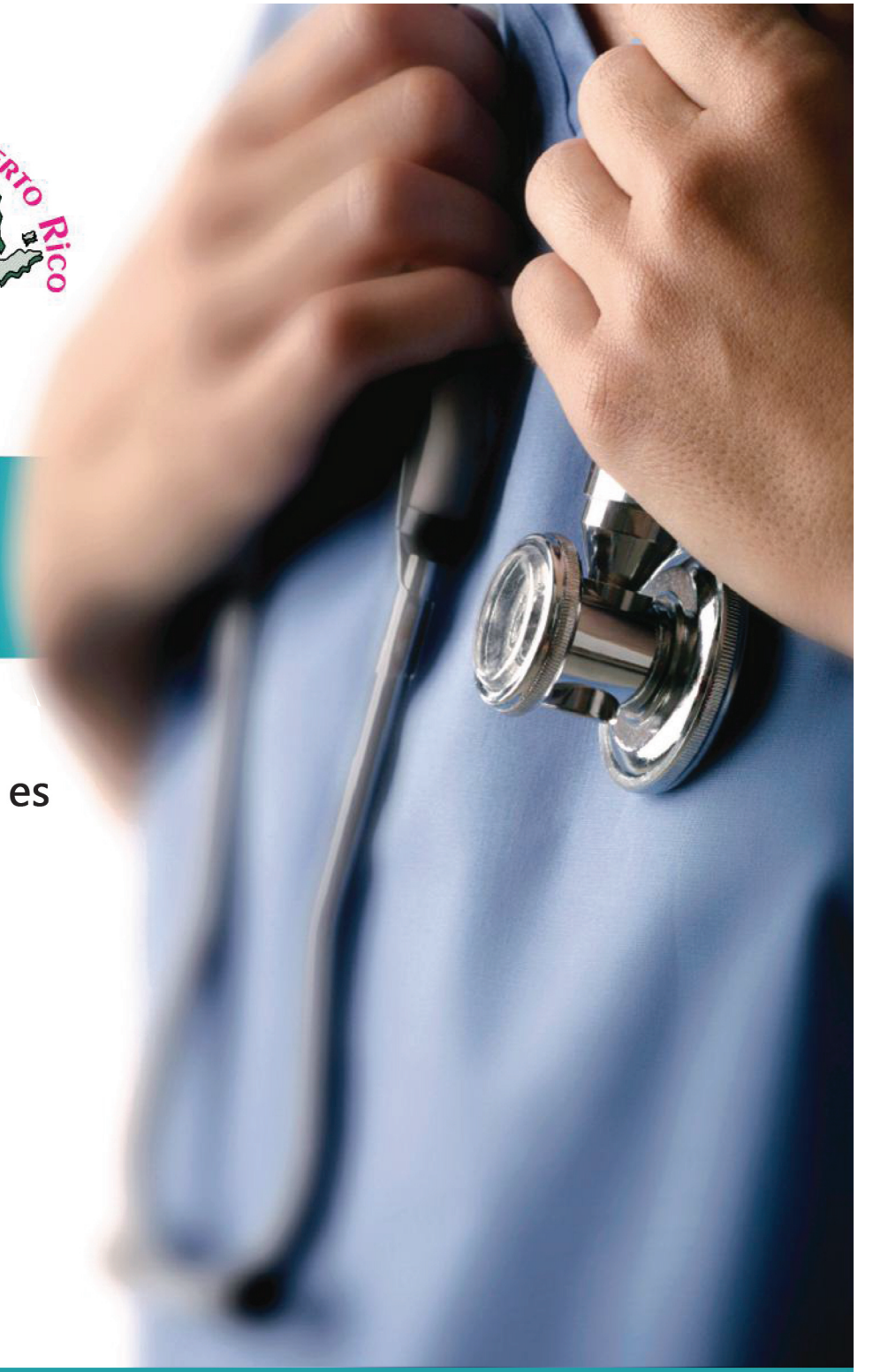

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