OCTUBRE - DICIEMBRE 2017

JOURNAL *of* the College of Physicians Surgeons of Puerto Rico

REVISTA DEL COLEGIO DE MÉDICOS CIRUJANOS DE PUERTO RICO

CONTENIDO

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CONTENIDO

Octubre - Diciembre 2017

High Dose Nitroglycerine in Hypertensive Cardiogenic Pulmonary Edema: How to Preclude a Respiratory Failure

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ABSTRACT

Background Hypertensive cardiogenic pulmonary edema (HCPE) is a hyperacute complication of congestive heart failure (CHF) and is defined as the accumulation of fluid in the lung, secondary to an abrupt increase of hydrostatic pressure that causes extravasation of fluid from the lung circulation into the interstitium.

Case Report Case of a 63-year-old Hispanic male that arrived at the emergency room complaining of severe dyspnea that began 30 minutes before arrival. Patient management included high dose nitroglycerin IV after 18 minutes of aggressive therapy, patient improved with no need for mechanical ventilation.

Conclusion Several studies have demonstrated the benefit of high dose nitroglycerine over high dose diuretics for the acute management of HCPE. Our purpose is to emphasize the advantages of using this approach early on in this condition.

Key words Heart failure, Pulmonary edema, Nitroglycerin, Furosemide

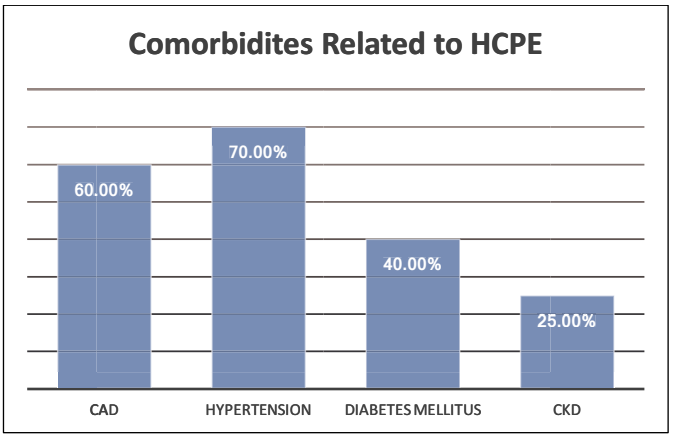
INTRODUCTION

Hypertensive cardiogenic pulmonary edema (HCPE) is a hyperacute complication of congestive heart failure (CHF) defined as the accumulation of fluid in the lungs secondary to an abrupt increase in hydrostatic pressure that causes extravasation of fluid from the lungs circulation into the interstitium [1]. HCPE presents with severe symptoms of tachypnea, hypertension, breathing difficulty and hypoxemia that can lead to an imminent acute respiratory failure. Although the presentation of HCPE is similar to acute decompensated heart failure, these two should not be confused presents with a more gradual onset of symptoms.

HCPE has an incidence of 10/1000 and poses a high prevalence of over 5 million patients in the United States, representing over 1,000,000 admissions annually [2-4]. Patients with HCPE represent 25% of CHF patient admissions or over 250,000 annually in the United States with a high mortality rate ranging from 15%-20% [5-6]. Particular attention should be paid to the elderly population, in view that the median age for acute pulmonary edema is 74 years [7]. Patients often present with multiple comorbidities: elevated blood pressure and coronary artery disease are the most common [8] (Chart 1).

The management of HCPE has undergone several transformations, and the key to understanding the newer

Chart 1:



CAD: coronary artery disease CKD: chronic kidney disease

approaches is a clear understanding of the pathophysiology of HCPE. HCPE as defined before causes extravasation of fluid from the lung circulation into the alveolar space and interstitium that builds up as transudate, and it is explained by the Starling relationship formula [9] (Figure 1). The normal pulmonary capillary wedge pressure (PCWP) ranges from 8-12 mm Hg, and normal colloid oncotic pressure is 25 mm Hg [10-11]. The cardiac output is reduced due to the left atrial impairment or left ventricle dysfunction, transmitting the increased pressure backward into the pulmonary capillaries; the increasing PCWP will exceed the oncotic pressure and the accumulating fluid results in pulmonary edema, overt hypoxia and the hindering of gas exchange. The cardiac output will not sufficiently supply the metabolic needs, increasing catecholamine levels, systemic vascular resistance and blood pressure with a further increase in the end-diastolic pressure and PCWP (Figure 2).

This pathophysiology can be triggered by the following etiologies: acute exacerbation of left ventricular dysfunction, cardiac ischemia, severe elevated blood pressure, aortic and/or mitral valve dysfunction and acute dysrhythmias. It must be noted that fluid overload is not mentioned as an etiologic cause. Although patients with HCPE have increased filling pressure, only 50% results in minimal weight gain and do not develop in to fluid [12-13]. Regardless of the etiologic origin, increased pressure will trigger the pulmonary capillary pressure, which must be handled by altering the base preload and afterload at the same time.

REPORT

A 63-year old Hispanic male patient presented with a medical history of hypertension of 20-year evolution, coronary artery disease and the placement of one coronary stent 5 years prior to the visit, Diabetes mellitus type 2 of 15 year duration, chronic kidney disease stage 3B, and heart failure with reduced ejection fraction (EF:35%) New York Heart Association stage II of 10 year evolution. The patient was being managed with carvedilol 25 mg twice daily, lisinopril 20 mg daily, spironolactone 25 mg daily, furosemide 20 mg daily, glargine insulin 20 units at bedtime, lispro insulin 7 units three times a day, atorvastatin 40 mg daily and aspirin 81 mg po daily and had no known drug allergies. The patient was in his usual state of health, asymptomatic until 30 minutes before arrival to the emergency room when he reported sudden onset of severe respiratory distress, palpitations and profuse diaphoresis. Triage vital signs were remarkable for blood pressure: 205/110 mm Hg, respiratory rate: 29, heart rate: 118 beats per minute, pulse oximetry: 82% on room air, temperature: 36.2 0C, weight: 72 kg, height: 68 inches, BMI: 24.13 kg/m2. On physical exam, the patient is remarkable for severe respiratory distress, diaphoresis and was unable to talk in complete sentences. Jugular vein distention (JVD) was noted as 3+ along with abdominal and intercostal retractions. Profuse bilateral inspiratory crackles were auscultated in all pulmonary fields. Cardiac auscultation was remarkable for a gallop with a regular rate along with a systolic murmur 3/6 noticed at the left midclavicular line at the 5th intercostal space. The point of maximal impulse was displaced to the left at the anterior mid-axillary line and neither abdominal distention nor ascites were noted, but lower limb pitting edema 1+ was noted up to the mid- shin.

The patient was placed in the intensive care area as air blood gases, labs and non-rebreather mask at 100% oxygen were ordered, and the patient was positioned at 900. Immediate observation showed pulse oximetry increased up to 90% (Table 1). Electrocardiogram revealed sinus tachycardia, lateral lead ST depression of 1 mV, left axis deviation and left ventricle hypertrophy. A portable chest x-ray was obtained with augmented cardiac silhouette, cephalization or stag's antler sign, and Kerley B lines (Figure 3). The patient was critically ill, and further management could not be delayed until lab results returned, thus the initial treatment was guided based on clinical history, EKG, ABGs and x-ray findings. Absence of fever, characteristic sudden onset and remarkable JVD pointed away from a pneumonic process and management for a hypertensive cardiogenic pulmonary edema was immediately started. Nitroglycerine IV was ordered, starting at 30 mcg/min and increased by 15 mcg/min every 3 minutes, along with continuous pulse oximetry and constant vital sign check every 3 minutes. After 18 minutes, nitroglycerin was titrated up to 120 mcg/min and the blood pressure decreased to 148/82 mm Hg, systolic blood pressure showed a reduction of 29% and the diastolic blood pressure showed a reduction of 25% and the heart rate decreased to 87 beats per minute. A drastic clinical improvement was noted: the patient was able to communicate in complete sentences and neither intercostal retractions nor accessory muscle use was noted. Pulse oximetry maintained saturation over 97%, the oxygen supplementation was decreased to 3 L/min via nasal cannula and patient continued with a pulse oximetry over 96%.

After 25 minutes, the patient was administered enalapril at 2.5 mg IV combined with furosemide 20 mg IV. Nitroglycerine was decreased at a rate of 10 mcg/min every 5 minutes until it was discontinued, followed with an oral dose of 30 mg of isosorbide dinitrate. Our patient was evaluated with Well's score for pulmonary embolism (PE) and was determined as low risk. D-dimer levels also returned negative, effectively ruling out the diagnosis of pulmonary embolism. Further evaluation for

hyperthyroidism showed an adequate ultra-sensitive thyroid stimulating hormone (usTSH), triiodothyronine (T3) and free thyroxine (free T4). The patient was admitted to the internal medicine ward with the diagnosis of hypertensive cardiogenic pulmonary edema and was discharged home 48 hours later with the following medications: furosemide 40 mg daily, carvedilol 12.5 mg twice a day, sacubitril/valsartan 24 mg/26 mg twice a day, spironolactone 25 mg daily and isosorbide mononitrate 60 mg daily. The cardiologist then followed the patient weekly for optimization of medication therapy. No emergency room visits or hospitalizations were reported for the next 60 days.

DISCUSSION

The most common causes of heart failure exacerbations include: medication noncompliance, symptomatic anemia, arrhythmias, ischemia, life style habits, cardiac output upregulation, renal failure and pulmonary embolism. Our patient developed a flash cardiogenic pulmonary edema due to non-compliance resulting in his severe hypertension and triggering his heart failure exacerbation. This presentation is especially worrisome in the emergency department, as patients are desperate and management must start immediately based on medical history, physical exam and chest x-ray. Unfortunately, the sensitivity of these findings is less than 70% [13]. Our patient presented with the classic physical findings of hypertensive cardiogenic pulmonary edema: crackles on auscultation, JVD, severe acute dyspnea (air hunger), elevated blood pressure and was managed accordingly with high dose nitroglycerine. We must remark that our patient was not managed with furosemide. Furosemide has long been considered the cornerstone management of HCPE but now has been replaced by other drugs. Today, physicians hold a broad pharmacologic arsenal against HCPE, but only a few drugs require no dose modifications and retain the necessary pharmacologic characteristics to be considered the cornerstone and almost the standard of care (Table 2). Those characteristics should include a rapid onset, titratable dosing based on patient response, predictable effect, short half-life and a mechanism of action that blocks several pathways in the pathophysiology of this disease. During the acute phase of HCPE the pathology augments the compensatory mechanisms: activation of the renin-angiotensin-aldosterone system (RAAS), increasing the myocardial contractility and activating the adrenergic system.

PRELOAD

Otto Frank and Ernest Starling can be considered pioneers in cardiac physiology, being first to describe the relationship between end-diastolic volume and ventricular performance. The end-diastolic volume, also known as the preload, can be defined as the filling pressure of the heart at the end of the diastole which is intrinsically related to myocardial distention. The preload can be assessed from left ventricle end diastolic pressure with an invasive (cardiac catheterization) or a non-invasive study (echocardiography), and must not be confused with venous return [14]. Venous return is defined as the amount of blood returned from the periphery to the right atrium and is related to cardiac output [15]. Cardiac output can be defined as the amount of blood volume being pumped by the heart for 1 minute. Under normal circumstances, the venous return matches the cardiac output. In the event of augmented end-diastolic volume, a normal heart will proportionally increase the stroke volume in a compensatory manner. Conversely, increased preload in a heart with impaired function will not be able to increase the stroke volume efficiently, causing a retrograde augmentation of pressure which is translated into increased pulmonary hydrostatic pressure, as occurs in HCPE. Although preload is elevated in HCPE, this type of evaluation is not needed for the initiation of treatment [16]. The initial treatment aim is to reduce the preload and subsequently reduce the pulmonary hydrostatic pressure, equalizing the cardiac output and the venous return. Several drugs historically work in this part of the heart failure cycle: nitroglycerine, morphine sulfate, loop diuretics and recombinant brain natriuretic peptide (BNP).

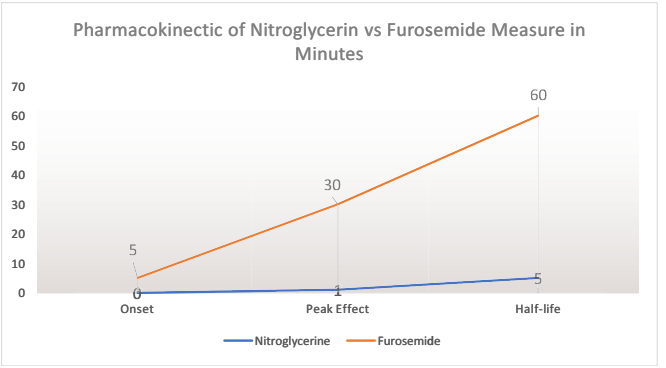
NITROGLYCERINE

Nitroglycerine is part of the family of nitro-vasodilators, which achieve their effect by donating a free radical nitric oxide to activate guanylate cyclase in the vascular smooth muscle leading to dephosphorylation of myosin light chain. As a result, nitroglycerine produces a marked vasodilator effect on veins and a modest vasodilator effect on arteries [17]. The venous vasodilator effect is translated into an increased venous capacitance, which causes a decreased venous return resulting in a reduction of preload as well.

There are several formulations of nitroglycerine including: sublingual tables, translingual spray, topical, transdermal patch and intravenous (IV). The topical and transdermal formulations are not recommended during HCPE because of the possibility of overload and profuse sweating which can cause an erratic absorption with unpredictable effects. We encourage the use of the IV formulation. Nitroglycerin IV possesses an immediate onset of action with an immediate peak effect. The duration is determined to be 3-5 minutes with a half-life of 1-4 minutes [18] (Chart 2).

Nitroglycerine is the most effective, predictable and rapid-acting drug for HCPE [19]. Several studies have compared the use of nitroglycerine, furosemide, and morphine and demonstrated the superiority of nitroglycerine [20]. The superiority of this drug relies on its rapid onset, rapid peak, and brief half-life, therefore

Chart 2:

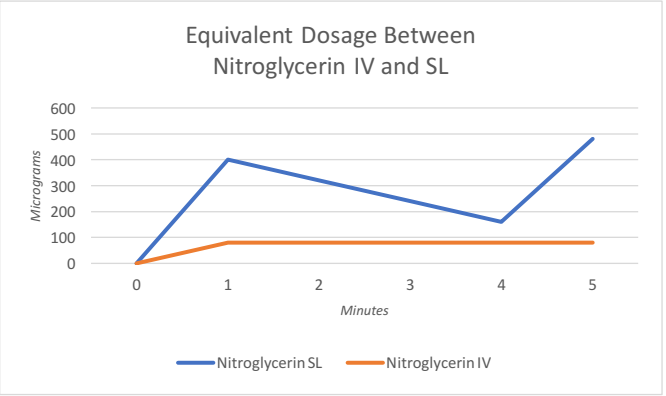


if a patient developed hypotension or another undesired effect, stopping the drug for 5-10 minutes will be sufficient to return to baseline.

Nitroglycerine dosing for HCPE from the one used for angina or ordinary heart failure. HCPE nitroglycerine dosing should be started at 20 mcg/min followed by a rapid titration of 15-20 mcg/min every 3-5 minutes with an average goal of 100 mcg/min and a maximum dose of 400 mcg/min. At these levels, nitroglycerine decreases the afterload as well [21-22]. If an infusion pump is not available, nitroglycerine can be administrated as 3 mg IV bolus every 5 minutes, as documented in one study, where 3 mg is equivalent to 600 mcg / min [23]. The usual anti-angina sublingual nitroglycerine 0.4 mg dose every 5 minutes for 3 doses is equivalent to ~80 mcg / min IV (Chart 3).

FUROSEMIDE

Chart 3:



Furosemide is a potent diuretic that belongs to the family of loop diuretics/high ceilings;, its mechanism is to inhibit the reabsorption of sodium and chloride in the thick ascending loop of Henle, proximal renal tubules and distal renal tubules which results in reduced preload. This diuretic has several formulations including: oral tablets and solution for intramuscular and intravenous use. When intramuscular and intravenous administrations are not possible, furosemide can be used sublingually. Although it can decrease blood pressure, loop diuretics including furosemide should not be used for hypertension treatment, as suggested by the Eighth Joint National Committee (JNC 8) [24]. The recommended use of furosemide is to treat edema associated with renal disease, heart failure disease, hepatic disease and pulmonary edema.

Although its mechanism is promising in the treatment of HCPE, its pharmacokinetics explain why it should not be considered as a monotherapy any longer. The onset of action averages 5 minutes for furosemide IV, the peak effect is at 30 minutes, and half-life is 60 minutes [25]. When furosemide is chosen for the treatment of HCPE, doses are high and aggressive: 40-80 mg IV bolus, with the consideration of a second bolus after 20 minutes if no improvement [26]. Although higher doses are related to symptomatic improvement, they are also related to worsening renal function and increased rate of admission to the intensive care unit [27]. Fifty percent of patients diagnosed with HCPE are due to fluid overload, and the rest are hypovolemic or euvolemic. Thus, the prescription of high dose furosemide will deteriorate renal function. Furthermore, the sympathetic and adrenergic states of HCPE increase systemic vascular resistance and renal vasoconstriction, affecting renal function [28]. Due to renal vasoconstriction, the peak effect will be considerably delayed, up to 45-120 minutes, beyond a reasonable framework to manage this pathology [29]. In addition, there are studies that stipulate that the use of furosemide during the initial phase of HCPE poses adverse effects due to activation of the renal angiotensin aldosterone system (RAAS) in response to the volume depletion. This activation of RAAS will further increase the mean arterial pressure (MAP), systemic vascular resistance and pulmonary capillary wedge pressure and result in a reduction of the cardiac output and stroke volume [30].

MORPHINE

Morphine is a part of the chemical class phenanthrenes, along with codeine and thebaine, and is still the standard to measure the efficacy of other opioids. Morphine is obtained from the poppy plant, Papaver somniferum. Morphine formulations include: tablets, suppository, and solution for intramuscular, intravenous and intrathecal. The most common indication is for severe pain control, but morphine can be prescribed in other conditions such as HCPE. When administered intravenously its onset of action ranges from 5-10 minutes, peak effect is at 20 minutes and half-life 2-4 hours [31].

One side effect of morphine is mast cell degranulation that releases histamine into the bloodstream resulting in vasodilation and further preload reduction, although there are no

randomized trials that support this observation [32-33]. The symptomatic improvement could be due to the reduction of sympathetic nervous activity resulting in an anxiolytic effect and reduction of dyspnea [27]. Despite being presumed to be the standard for reduction of preload, one study found 46% of patients diagnosed with HCPE and medicated with morphine resulted in objective clinical deterioration, while in another study patients showed an increased probability for intensive care unit admission and/or intubation [34-35]. Due to broad profile negative side effects like nausea, bronchoconstriction, pruritus and anaphylactoid reaction and the potential for clinical deterioration its use should be precluded and substituted by safer drugs such as low dose benzodiazepine.

AFTERLOAD

Afterload is closely related to aortic pressure and can be defined as the stress or tension in the left ventricle wall during contraction against peripheral vascular resistance. Patients suffering from HCPE have a catecholamine storm which increases the peripheral vascular resistance, resulting in decreased volume stroke and cardiac output. Thus patients will benefit from drugs that work in afterload reduction. High dose nitroglycerin can decrease the afterload but after a prolonged infusion (usually after 12-24 hours) patient can develop tolerance due to depletion of the enzymes responsible for the nitrate catabolism. Combination therapy with afterload reduction drugs is recommended.

ACE INHIBITORS

ACE Inhibitors (ACE-i) are drugs that inhibit the angiotensin-converting enzyme which precludes the conversion of angiotensin I to angiotensin II. The first synthesized drug of this family was captopril, which was discovered from the Brazilian viper, Bothrops jararaca [36]. Drugs of this family are prescribed for blood pressure control, preventing the progression of diabetic nephropathy and chronic heart failure with reduced ejection fraction, but can also be prescribed in acute decompensated heart failure and HCPE. ACE inhibitors work in the RAAS and modify cardiac remodeling in heart failure with reduced ejection fraction as a class effect. We will discuss enalaprilat, a metabolite of the prodrug enalapril after hepatic metabolism, due to broad evidence and convenient IV formulation.

ENALAPRILAT

Enalaprilat is the active metabolite of enalapril after hepatic metabolism. Enalapril does not need hepatic dose adjustment but does need a renal dose adjustment. Patients with HCPE do present with acute or chronic renal impairment, but the benefits outweigh the risk of its use. Premedication with nitrates will enhance, at least temporarily, the affected renal function via renal vasodilation and decrease the possible nephrotoxic effect of enalaprilat in the acute phase [37]. Due to its mechanism of action, ACE-i decreases the arteriolar efferent tone that is responsible for maintaining the glomerular filtration rate in the decreased renal perfusion state. This drug poses an onset of action ~15 minutes, peak effect at 1-4 hours, duration effect 6 hours and half-life of ~36 hours [38]. Benefits of ACE-i include the reduction of pulmonary capillary wedge pressure, improvement in stroke and cardiac output without affecting heart rate or drastic changes in mean arterial pressure, which reduces mechanical ventilation, intensive care unit admission, and length of stay [39-40]. ACE-i should be avoided in patients with a history of angioedema, even of unknown etiology and they should be used with extreme caution or not used in hypotensive patients and history of aortic stenosis.

NESIRITIDE

Nesiritide was primarily approved in 2001 for the reduction in pulmonary wedge pressure and indicated in acute decompensated heart failure. This drug is a recombinant brain natriuretic peptide with vasodilator properties and diuresis enhancement that improves cardiac output [41].

Nesiritide poses an onset of action of 15 minutes, peak effect of 1 hour, duration ~60 minutes and half-life of 2-18 minutes [42]. Several studies have been designed to evaluate the use of nesiritide in acute decompensated heart failure including the ASCEND-HF trial and VMAC trial. In the ASCEND-HF trial, dyspnea at 6 hours, dyspnea at 24 hours and the rate of rehospitalization / death at 30 days were evaluated. A small reduction without statistical significance in dyspnea was reported but there were no differences in rehospitalization / death at 30 days. The VMAC study included 498 patients and concluded that nesiritide does pose a significant effect on dyspnea at 3 hours, however, the effect was similar to intravenous nitroglycerin in that no significant effect is observed at 24 hours [43]. In these trials, most patients received average nitroglycerine dose of 30-40 mcg/min and did not receive optimal nitroglycerine dose for HCPE (over 100 mcg/min), because most physicians were reluctant to use those high doses [44]. In addition, another small trial that showed worsening of renal function by 1.5 times, but confidence interval was wide [45].

VENTILATION SUPPORT

Supplemental oxygen is not required unless oxygen saturation falls below 92%, because hyperoxemia will increase the circulation of free radicals, causing vasoconstriction and decreased cardiac output that may contribute to an increase in short term mortality [46-47]. There is no rule for the route of

oxygen support to be offered to the patient, it will rely on the patient needs. If oxygen saturation falls below 92%, oxygen can be initially supplemented via nasal cannula or Venturi mask, as long as the patient does not develop severe respiratory distress, acidosis or hypoxemia. Once supplemental oxygen is insufficient, non-invasive ventilation can be considered, including bi-level positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP) [48]. Several studies have postulated that the non-invasive ventilation decreases the length of stay in an intensive care unit, hospital cost and the need for invasive mechanical ventilation. Between non-invasive ventilation modes, the most recommended method is CPAP, based on a small head to head trial that concluded that patients managed with BiPAP improved more rapidly, but the rate of myocardial infarct was higher [49]. Furthermore, patients in the BiPAP arm of the trial initially reported more chest pain that in that of the CPAP arm and further studies did not show difference between those two non-invasive ventilation modes. We recommend the use of CPAP in patients with persistent hypoxia (less 92%) despite of supplemental oxygen and BiPAP in patients with history of chronic obstructive pulmonary disease. Mechanical ventilation is considered as the last resort when patient persists with hypoxia despite non-invasive ventilation or where there is a contraindication such as altered mental status, vomiting or non-compliance.

CONCLUSIONS

Physicians have a great variety of drugs to use for the treatment]=[[[[[[[[[[of HCPE, but few possess the pharmacokinetic characteristics to adequately manage this dire pathology. Several decades ago, furosemide was considered the cornerstone treatment in the management of HCPE, but today there is enough evidence to show the superiority of intravenous nitroglycerine pharmacokinetically and pharmacodynamically when prescribed for HCPE. Unfortunately, most physicians are reluctant to prescribe high dose nitroglycerine (over 100 mcg/min) and are still selecting to the use of high dose furosemide. High dose nitroglycerin could be considered a cost-effective therapy in view of evidence that this aggressive medication can preclude procedures like tracheal intubation, does not affect renal function nor increase intensive care unit admission rates compared to other drugs like furosemide.

When a physician is considering the use furosemide in HCPE, he must weigh the cardiovascular effects of this drug during HCPE like the sympathetic and hyper-adrenergic state. When its use is required, such as the presence of fluid overload, we recommend premedication with nitroglycerine and ACE-inhibitor and postpone prescribing furosemide until later, once the clinical stability has been achieved. This strategy can blunt the cardiovascular and renal adverse effect of furosemide [50].

Other newer drugs, such as nesiritide, were promising but are too expensive and show no superiority when compared with nitroglycerin. However, nesiritide is still suitable for the management of HCPE when nitroglycerine is contraindicated such as in the recent use of phosphodiesterase 5 inhibitors.

Unfortunately, cardiology associations and emergency medicine associations have not yet developed guidelines for the management of HCPE and current management is based on recommendations and clinical observations. There is enough evidence in controlled trials worldwide that will support the development of formal guidelines for the management of hypertensive cardiogenic pulmonary edema.

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Figures:
1. Frank Starling equation.
2. Summary of HCPE physiopathology.
3. Portable chest x-ray showing increased cardio-thoracic index, cephalization and interstitial edema.

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Patients with Hermansky-Pudlak Syndrome: A Vital Need for Co-management

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ABSTRACT

Importance Puerto Rico (PR) has the highest prevalence of patients with the Hermansky-Pudlak syndrome (HPS) in the world. All health professionals in PR need to be aware of the clinical manifestations of patients with the syndrome.

Observation Several studies have reported on the clinical findings of patients with the HPS, including ophthalmic, hematologic, pulmonary, gastrointestinal, gynecologic-obstetric and dermatologic complications..

Conclusion and relevance Patients with the syndrome may benefit from a multi-specialty co-management, steered by a primary physician.

Key words Hermansky-Pudlak Syndrome, HPS

ABSTRACTO

Importancia Puerto Rico (PR) has the highest prevalence of patients with the Hermansky-Pudlak syndrome (HPS) in the world. All health professionals in PR need to be aware of the clinical manifestations of patients with the syndrome.

Observación Varios estudios han reportado los hallazgos clínicos de los pacientes con HPS y sus complicaciones oftálmicas, hematológicas, pulmonares, gastrointestinales, gineco-obstétricas y dermatológicas.

Conclusion y relevancia Los pacientes con el síndrome se beneficiarían de un co-manejo de múltiples especialistas liderado por un médico primario.

INTRODUCTION

Hermansky and Pudlak syndrome first described two unrelated patients who had oculocutaneous albinism and bleeding diathesis.[1] Typically, patients with the syndrome have a triad including oculocutaneous albinism, bleeding diathesis, and manifestations associated with ceroid deposition in both the lungs and intestines.[2]

Previous studies have described the incidence of the disease in many countries, but the Hermansky-Pudlak syndrome (HPS) is the most common inherited disease in Puerto Rico. It is more prevalent in the northwestern quarter of the island.[3] However, due to large native emigration to the continental United States[4] in the last two centuries, the syndrome has also been reported in Puerto Rican descendants on the mainland.[5]

HPS is transmitted as an autosomal recessive trait. Several genetic mutations may lead to the syndrome. Patients with three different types have been reported in Puerto Rico, namely HPS-type 1, HPS type 2 and HPS type 3.6. Even though genetic linkage analysis is available, diagnosis remains clinical, due to the various mutations that may lead to the syndrome.

Due to the various clinical manifestations and surgical complications in patients with the syndrome, both primary physicians and specialists need to be aware of the disease. For this reason, a review of the signs and symptoms of patients with HPS is desirable.

OPHTHALMIC FINDINGS

Several studies[7,8] have reported that patients with the syndrome have ophthalmic findings including poor vision, refractive errors, nystagmus, strabismus, iris transillumination, foveal hypoplasia,[9] albinotic retinal mid-periphery and abnormal decussation of the optic nerve fibers.

Pre-senile cataracts have been reported in patients with the syndrome. Its etiology remains unknown. Dávila and co-workers[10] have reported that patients with the syndrome may undergo cataract surgery and intraocular lens implantation to improve vision and thus quality of life. The advent of smaller incisions and topical anesthesia has decreased surgical risks in patients with the syndrome. However, pre-operative evaluation by several specialists is of utmost importance in patients with HPS.

HEMATOLOGIC COMPLICATIONS

Bleeding diathesis increases morbidity and mortality in patients with HPS. Even though patients with this syndrome have a normal platelet count, electron microscopy studies[11,12] have shown either lack or decreased dense granules. Platelets do not adhere in patients with the syndrome, hence they have prolonged bleeding times. Both PT and PTT show normal values. For these reasons, patients with the syndrome should not take aspirin, medications containing aspirin, or non-steroidal anti-inflammatory agents.

Desmopressin test should be done in patients with the syndrome, as not all respond to desmopressin therapy for bleeding tendencies.[13,14] Some patients benefit from aminocaproic acid.15 Others may need platelet transfusion or plasma apheresis. Unfortunately, these therapeutic modalities are costly. For these reasons, patients with the syndrome should be evaluated by a Hematologist prior to surgical procedures. Platelets may be transfused in some ambulatory settings prior to surgery in patients with HPS, producing an elevated quantity of antibodies.

PULMONARY COMPLICATIONS

Patients with HPS type 1 have a higher risk of pulmonary complications. They may develop interstitial disease and pulmonary fibrosis.[16,17] Broncho-alveolar lavage studies have shown ceroid-laden macrophages in patients with the syndrome. For this reason, pulmonary fibrosis was thought to occur secondary to abnormal ceroid deposition. Recent studies have suggested that intra-alveolar bleeding could be another causative factor.

Primary physicians should advise patients with the syndrome to avoid both active and passive smoking. Kelil and co-workers[18] have suggested that pulmonary function tests are warranted in patients with HPS. Some will need oxygen, pulmonary rehabilitation and pulmonary transplants. For these reasons, patients with the syndrome may benefit from co-management with a pneumologist.

Steroids were used in the past to treat patients with pulmonary fibrosis. Recent studies of pirfenidone[19] to halt fibrosis in patients with the syndrome are inconclusive, and its use in patients with HPS remains off-label. Further studies evaluating this medication for patients with the syndrome are warranted.

GASTROINTESTINAL COMPLICATIONS

Gastrointestinal complications have been reported in patients with HPS, being more common in those with type 3 mutation.[20-22] Both ulcerative and a Crohn´s-like granulomatous colitis have been reported in patients with the syndrome. Patients with HPS may have upper or lower gastrointestinal bleeding, and fistulas. Erzin and co-workers[23] reported a patient with HPS that was complicated by granulomatous colitis with perineal and rectovaginal fistulas refractory to antibiotics and azathioprine, who dramatically responded to repeated infusions of infliximab.

Patients with procto-colitis may need surgical management.[22] Primary care providers should be aware of gastrointestinal complications in patients with the syndrome, so the latter may benefit from co-management with gastroenterologists and colorectal surgeons.

OB-GYN COMPLICATIONS

Previous studies[24] have reported that female patients with the syndrome have menorrhagia. Van Avermaete and co-workers[25] have reviewed the obstetrical complications in patients with the syndrome. Since most patients with HPS reach reproductive age, all physicians need to be aware of these complications and manage patients accordingly.

DERMATOLOGIC COMPLICATIONS

Phenotypic variability remains the most prominent finding in patients with the syndrome.[26] Both hair and skin coloring varies considerably among these patients. For example, patients with HPS type 3 have darker hair, skin and iris pigmentation compared to patients with HPS type 1.

Unfortunately, skin malignancies have been reported with oculocutaneous albinism.[27] Primary physicians should evaluate both sun-exposed and non-exposed skin in patients with the syndrome, and a consultation with a dermatologist may be needed for suspicious skin lesions. Preventive measures, such as avoiding direct sun exposure and sunscreen protection are of utmost importance in skin care of patients with the syndrome. Questionable skin lesions should be biopsied and treated as needed.

Interestingly, Ikawa and co-workers[28] first demonstrated that lentiviral-mediated gene transfer corrects the expression and function of the HPS1 gene in patient dermal melanocytes, which opens the way to development of gene therapy for HPS.

DISCUSSION

The Hermansky-Pudlak syndrome is a rare genetic disease, which is relatively common in Puerto Rico. There are several mutations associated with it and additional studies are warranted to further characterize the condition and understand its pathophysiology, response to treatment, and prognosis.

To the best of our knowledge this is the first review suggesting that patients with the syndrome should be co-managed with a pyramidal system of primary care providers and sub-specialists network since childhood. Both primary care physicians and specialists must be aware of both early and late-onset manifestations of patients with Hermansky-Pudlak syndrome, to prevent complications and improve their quality of life.

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Cáncer de Cabeza y Cuello y Virus del Papiloma Humano

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Summary
The incidence of head and neck cancer caused by the Human Papilloma Virus (VPH) has been increasing and it's expected to surpass the incidence of cervical cancer in women by 2020. Robotic transoral surgery has evolved to be an integral part of the standard of care in patients with throat cancer with excellent results.

Resumen
La incidencia de cáncer de cabeza y cuello causado por el virus del papiloma humano (VPH) ha ido aumentando y se espera que para el 2020 sobrepase la incidencia de cáncer cervical en la mujer. La cirugía robótica transoral ha evolucionado a ser parte integral en el estándar de cuidado del paciente con cáncer de garganta con excelentes resultados oncológicos.

ETIOLOGÍA E INCIDENCIA

El cáncer de cabeza y cuello es el quinto cáncer más común entre la población general en Puerto Rico. La clasificación de cáncer de cabeza y cuello se divide de la siguiente manera: cavidad oral (i.e. lengua, paladar duro, piso de boca), orofaringe (paladar blando, amígdalas, lengua posterior) y laringofaringe (garganta), piel, glándulas salivares y tiroides. Cuando hablamos de cáncer de cabeza y cuello la histología más común es cáncer de células escamosas (squamous cell carcinoma). Mayormente, cuando hablamos de que un paciente tiene este tipo de cáncer nos referimos a que tiene un cáncer de tracto aerodigestivo (i.e. lengua, amígdalas, o garganta entre otros sitios).

En las estadísticas del registro de cáncer de Puerto Rico se reportó, entre 2006 y 2010 una cifra de 1,919 casos de cáncer de cavidad oral y orofaringe. A través de la historia estas malignidades eran relacionadas al tabaquismo, abuso de alcohol y a la pobre higiene dental. Usualmente, estos son tumores que se presentan en pacientes mayores de 60 años. En los últimos 20 años, sin embargo, hemos visto un factor de riesgo nuevo para cáncer de cabeza y cuello llamado el virus del papiloma humano (VPH). Estos pacientes con cáncer relacionado a VPH son, generalmente, hombres profesionales de edad productiva.

Cáncer de Cabeza y Cuello y Virus de Papiloma Humano

El cáncer de cabeza y cuello va en aumento en las áreas de amígdala y la base de lengua donde la causa principal de este es el virus del papiloma humano (VPH), el mismo virus que causa cáncer en el cérvix de la mujer. El Instituto Nacional de la Salud (NIH) estima que para el 2020 la incidencia del cáncer de cabeza y cuello relacionado a virus de papiloma humano será mayor que la de cáncer cervical de la mujer.

La sobrevivencia relacionada al cáncer de cabeza y cuello se ha mantenido estable por sobre dos décadas, pero se ha visto mejorada para el subgrupo de pacientes con tumores relacionados al VPH.

El tratamiento de esta condición usualmente consta de una sola modalidad de terapia (cirugía o radio terapia) para cáncer de estadío temprano. En cáncer avanzado el tratamiento usualmente es una combinación de cirugía con radioterapia y/o quimioterapia, cuando es indicado.

Las malignidades de esta región se trataban con radiación y quimioterapia o cirugías abiertas a lo largo de 20 años. Los resultados de la sobrevivencia entre las dos modalidades de tratamiento son comparables 4,5, pero la cirugía abierta a través de la mandíbula resultaba en una morbilidad alta para el paciente ya que había que dividir la mandíbula para tener acceso adecuado al área posterior de la garganta.

En comparación, la radioterapia y la quimioterapia se pueden dar como tratamiento alternativo con un buen resultado oncológico sin la intervención de cirugía. Sin embargo, la toxicidad que conllevan la radioterapia y la quimioterapia en los pacientes jóvenes[6] que tienen una esperanza de vida prolongada nos inclinan, con frecuencia, a preferir la cirugía robótica sobre otras modalidades de tratamiento. Algunos de los efectos adversos de la radioterapia y la quimioterapia son dificultad progresiva para tragar, endurecimiento de los tejidos del cuello, y hasta muerte causada por supresión del sistema inmunológico por quimioterapia entre otros.

La cirugía robótica transoral de cabeza y cuello (TORS – por sus siglas en inglés) fue aprobada por el FDA en el 2009 con el sistema DaVinci® para tumores benignos o cancerosos de estadío temprano en la amígdala y base de la lengua. La cirugía TORS se desarrolló como una herramienta mínimamente invasiva para manejar quirúrgicamente estos tumores. En el presente el sistema de robótica que se utiliza es el DaVinci S®, el cual está disponible en Puerto Rico. Este sistema ha evolucionado hasta ser parte del estándar de cuidado en los grandes centros de cáncer de Estados Unidos, Europa y Asia para operar tumores de la orofaringe (i.e. amígdala, base de la lengua). La diferencia entre la cirugía robótica versus la cirugía tradicional es el acceso a través de la boca para poder alcanzar áreas que son difíciles de visualizar con los métodos tradicionales. Como explicado antes, en el pasado había la necesidad de dividir la mandíbula en la línea media para llegar hasta el área de la amígdala y la base de la lengua. Eran cirugías que usualmente duraban de 6 a 8 horas y la morbilidad era muy alta y representaba para el paciente una estadía prolongada de dos o tres semanas, con la necesidad de utilizar una traqueostomía (tubo para respirar por el cuello) con un impacto significativo en la función de tragar y hablar por el defecto creado.

La cirugía robótica transoral ha sido desarrollada para disminuir la morbilidad de la cirugía tradicional para el paciente. La cirugía con el DaVinci dura de 2 a 4 horas y el paciente usualmente no necesita una traqueostomía. Además, puede comenzar la ingesta de alimentos por la boca el día siguiente. Algunos pacientes pueden requerir radioterapia o combinación de quimio y radioterapia para garantizarle una cura al paciente. Sin embargo, estudios recientes han sugerido que podemos disminuirle la dosis de la radioterapia a muchos de estos pacientes con resultados oncológicos comparables. Al momento se están desarrollando nuevos estudios a nivel mundial, que van a buscar confirmar esa sugerencia.

En conclusión, la cirugía de cáncer de cabeza y cuello ha evolucionado hacia la introducción de los métodos menos invasivos para resolver estos problemas con mejores resultados y con menos morbilidad para el paciente.

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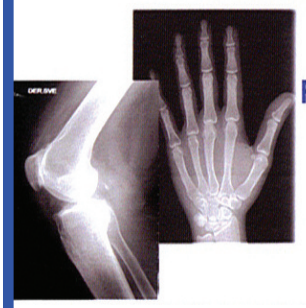

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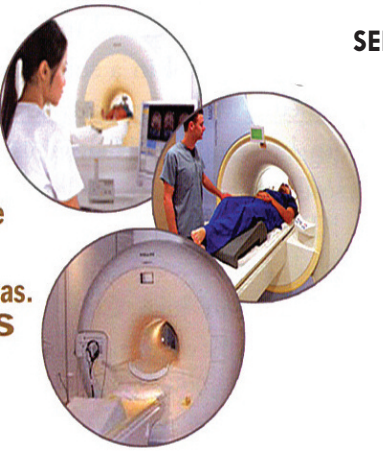

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An Unconventional Treatment for Severe Leptospirosis

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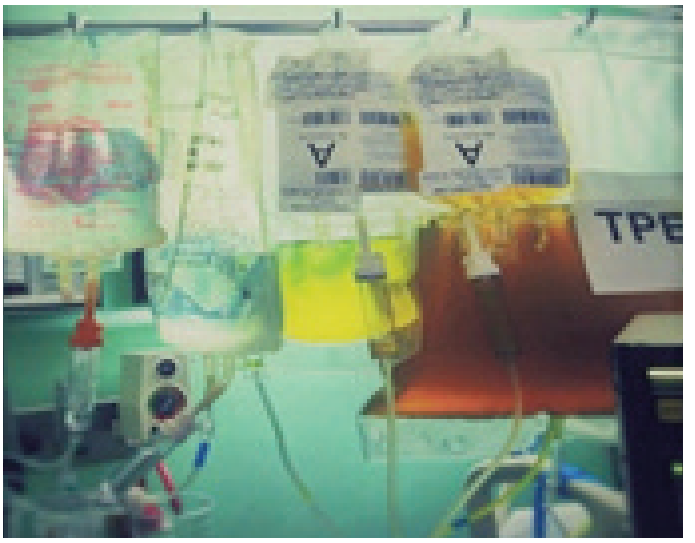
INTRODUCCION

La Leptospirosis es una infección bacteriana causada por una espiroqueta patogénica encasillada dentro del género de la Leptospira. Esta infección es causada por la exposición humana con la orina o tejido del animal infectado, siendo esta bacteria encontrada en el suelo y agua. Se estima que se infectan por Leptospirosis cerca de 0.1 a 1 por cada 100,000 personas cada año, pero esta cifra puede aumentar desde 10 a 100 por cada 100,000 personas cuando ocurren epidemias. El curso clínico de la Leptospirosis varía y esta puede ser confundida con otras enfermedades. Los síntomas más comunes incluyen fiebre, dolor de cabeza, temblores, dolor muscular, vómito, ictericia, anemia, y a veces erupción en la piel. Cuando la Leptospira no es tratada, puede producir fallo hepático con ictericia, fallo renal, meningitis, distrés respiratorio y como consecuencia un desenlace fatal. El tratamiento convencional de la Leptospirosis es principalmente con antibióticos y en su gran mayoría es auto limitante, pero tratamientos poco convencionales como la plasmaféresis, han demostrado ser efectivos en casos severos.

INTRODUCTION

Leptospirosis is a bacterial infection caused by a pathogenic spirochete of the genus Leptospira, resulting from exposure to an infected animal's urine, tissue, or contaminated water or soil. It is estimated that 0.1 to 1 per 100,000 people are affected each year, and can increase from 10 to 100 per 100,000 people during an epidemic. The clinical course of Leptospirosis varies and can be confused with other illnesses. Common symptoms include fever, headache, chills, muscle aches, vomiting, jaundice, anemia, and sometimes a rash. Left untreated, it can lead to liver failure with jaundice, renal failure, meningitis, respiratory distress and death. The treatment of Leptospirosis consists of antimicrobial therapy, and in most cases can be self-limited, but unconventional treatments such as plasmapheresis have shown to be beneficial in treating severe cases.



Treatment of Leptospirosis with Plasmapheresis in the Intensive Care Unit at the Hospital Universitario Ramón Ruiz Arnau, Bayamón, Puerto Rico

CASE PRESENTATION

Case of a 24-year-old man with no prior medical history complaining of fever, chills, joint pain, muscle aches, right upper quadrant abdominal pain, watery diarrhea, nausea, anorexia, and jaundice for the past 6 days. Patient lives near a river, owns a dog who is not properly vaccinated, has seen rats near his home, and has been working for the past two weeks scraping and repainting fences. Upon initial evaluation: Vitals: BP: 70/40 mmHg HR: 123 bpm Temp:

38.5° C RR: 26/min. Patient appeared acutely ill, febrile, with generalized jaundice, icteric sclera, epigastric and right upper quadrant tenderness with a palpable liver, and muscle tenderness. Labs reported White Blood Cells:17.11 10^3/uL; Hemoglobin:13.1g/dL; Platelets:14 10^3/uL; Creatinine: 2.1mg/dL; GFR:309; Sed Rate:98mm/h; CPK Total:3,835 IU/L; LDH:403; Direct Bilirubin:8.51 mg/dL; Total Bilirubin:10.32mg/dL; AST:133 IU/L; ALT:30 IU/L; HIV, Epstein Barr, and Hepatitis were negative, Leptospira IgM Ab: Reactive and Leptospira DNA QL PCR Urine: Detected. Abdominal Sonogram: Unremarkable. A clinical diagnosis of Leptospirosis was made, and Cefotaxime IV was initiated. By day 3 of treatment patient's renal function continued to decline, platelet levels did not improve, and bilirubin continued to rise (Creatinine:5.3mg/dL; GFR:13; Total Bilirubin: 14.88mg/dL; Platelets: 12 10^3/uL). Hematology service was consulted and plasmapheresis was initiated. After one session patient's labs showed signs of improvement and after 6 consecutive sessions, patient's renal function and platelets had normalized.

DISCUSSION

A clinical diagnosis of Leptospirosis can drastically impact patients' outcomes and prognosis. Symptomatic patients with Leptospirosis should receive antibiotic therapy which has been shown to decrease the duration of the illness and reduce the shedding of the organism in the urine, thus reducing the risk of developing severe complications. In adults, Leptospirosis is generally treated with either Doxycycline, Azithromycin, Penicillin, Ceftriaxone or Cefotaxime. In the case presented, plasmapheresis was used as an adjunctive therapy when the patient did not respond to conventional management with Cefotaxime. The role of plasmapheresis on the treatment of Leptospirosis has not been fully defined, but it has shown beneficial results by contributing to the resolution of the toxic effects from the hyperbilirubinemia on the hepatocytes and tubular renal cells. Recent studies have considered the possibility that plasmapheresis may also prevent injury mediated by sepsis or by an unknown immune mechanism in severe Leptospirosis.

CONCLUSION

The early suspicion and clinical diagnosis of Leptospirosis allowed this patient to begin receiving the appropriate antibiotic therapy days before serologic test results were received. The use of plasmapheresis as an adjunctive therapy may have contributed to the prevention of multi-organ failure, thus decreasing the development of long term complications in this case of severe Leptospirosis with hyperbilirubinemia and acute renal failure. The high incidence of long term complications and mortality in cases of severe Leptospirosis makes considering unconventional treatments such as plasmapheresis, vital for improving outcomes.

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Cryoglobulinemia of Unclear Etiology as an Anticipatory Presentation of a Future Neoplastic Process

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ABSTRACT
Retiform purpura involves a complete blockage of blood flow in the dermal and subcutaneous vasculature that results in purpuric lesions. A wide spectrum of differential diagnosis has been described, which always makes the search of its etiology a clinical challenge. Case of a 63-year-old female with medical conditions of arterial hypertension, and diabetes mellitus type 2, presented to our clinics with progressively worsening purpuric skin lesions. Physical exam was remarkable for multiple, non-blanching, purpuric ecchymosis. A biopsy of the lesions showed leukocytoclastic vasculitis with thrombosis of small vessels. Initial workup was unremarkable for cryoglobulins, ANA, anti-cardiolipin Ab, rheumatoid factor, C-ANCA, P-ANCA, Hepatitis panel, Protein C, Protein S and PT/PTT. The patient was admitted to the hospital where laboratory tests were repeated and found remarkable for positive cryoglobulins, strongly positive anti-citrullinated peptide, and positive rheumatoid factor levels. Abdominopelvic and thoracic imaging studies were found negative for any suspicious lesion. Although initial imaging studies were found negative, the patient's widespread distribution of lesions, presence of leukocytoclastic vasculitis on histopathology, and unclear etiology led us to consider the possibility of a paraneoplastic vasculitis. Since confirmatory evidence was not obtained, she was diagnosed with cryobulinemic vasculitis which was successfully treated. Though initial workup was unremarkable, a high degree of diagnostic suspicion for cryoglobulinemia prompted re-testing which was then found to be positive. This reflects the importance of re-testing when a high clinical suspicion based on history and physical examination is present. Effective diagnostic testing is of great importance in order to avoid complicated laboratory evaluations, multiple specialist referrals, and delay of treatment.

Key words
Retiform purpura, paraneoplastic vasculitis, cryoglobulinemia, re-testing, challenging diagnosis.

INTRODUCTION

Retiform purpura (RP) results from the complete blockage of blood flow in the dermal and subcutaneous vasculature with subsequent hemorrhage in a branched or angulated configuration [1]. Vasculitis and microvascular occlusion caused by thrombotic, infectious, or embolic phenomena have been described as the major causes of RP. However, many etiologies fall into the diagnostic umbrella of microvascular occlusion syndromes such as cryoglobulinemia, antiphospholipid syndrome, calciphylaxis, heparin necrosis, disseminated intravascular coagulation, protein C and S deficiency as well as cholesterol emboli among others. Hence, in addition to the infrequent clinical presentation, the wide spectrum of differential diagnosis makes RP an often-diagnostic challenge [1].

Cryoglobulins are immunoglobulins that precipitate in vitro at temperatures below 37 °C. Cryo- globulinemic disease or cryoglobulinemic vasculitis are terms used to describe patients with symptoms related to the presence of cryoglobulins in serum [2]. The percentage of patients with circulating cryoglobulins who develop symptoms varies from 2% to 50% [3]. Although most frequent causes of cryoglobulinemia are infectious, autoimmune, and lymphoproliferative disorders, nearly 10% of cases of mixed cryoglobulinemia are considered as either idiopathic or essential. In the particular cases of Rheumatoid Arthritis (RA) and Systemic Lupus Erythematous (SLE), it has been described that nearly 10% of these patients have a positive serology for cryoglobulins, but manifestations of RP are much less common than with other autoimmune diseases such as Sjogren's syndrome [4].

Although a rare entity, paraneoplastic vasculitis represents an important diagnosis that should be considered when evaluating a patient with an unusual cutaneous manifestation. Vasculitis has been previously reported associated with development of malignancy [4]. The most common solid tumors associated with vasculitis are lung, prostate, colon, breast, and renal carcinoma [6]. However, paraneoplastic polyarthritis with positive anti citrullinated peptide (anti-CCP) has also been described [7].

We report a rare case of a woman presenting with RP and diagnosed with essential cryoglobulinemia. The combination of a negative workup for common causes of cryoglobulinemia,

a strongly positive anti-CCP, histopathologic findings and widespread cutaneous lesions led us to consider paraneoplastic vasculitis as the likely cause of cryoglobulinemic syndrome.

CASE PRESENTATION

We present a case of a 63-year-old female with medical conditions of arterial hypertension, and diabetes mellitus type 2, complaining of progressive development of purpuric lesions of 1 month of evolution. Patient stated that lesions started in lower extremities and progressed to involve her buttocks, upper extremities and ears. She denied any systemic symptoms such as joint pain, fever, general malaise, weight loss. Physical examination was remarkable for multiple non-blanchable purpuric ecchymoses, many of them with central necrosis and erythematous borders, most assumed a retiform pattern (Figure 1). Additionally, she mentioned being evaluated by multiple specialists with no clear diagnosis made; therefore, she was referred to dermatology clinics. Upon clinical evaluation, biopsy of lesions was performed, showing leukocytoclastic vasculitis with thrombosis of small vessels (Figure 2). Specific work up including cryoglobulins, antinuclear antibody (ANA), antineutrophilic cytoplasmic antibodies (ANCA), hepatitis panel, and urine analysis were all performed and found unremarkable. However, in view of progressive development of lesions and still uncertain etiology, patient was sent to our hospital for further evaluation by rheumatology, hematology and oncology services.

Tests performed previously were repeated and additional work up was performed including: urine electrophoresis, Sjogren's antibodies, rheumatoid factor, anti-citrullinated peptide, protein S and C activity, echocardiogram, abdominopelvic and thoracic CT scans. Diagnostic laboratories were found to be remarkable for positive cryoglobulins, strongly positive anti-citrullinated peptide (>250 units) and positive rheumatic factor levels. Though no evidence of a malignancy was found, the possibility of a paraneoplastic vasculitis could not be ruled out. Although this seemed a diagnostic possibility, the supporting evidence was still incomplete; hence, it was concluded that she presented with cryoglobulinemic vasculitis. Consistently, patient was successfully treated with prednisone and eventually changed to a steroid sparing treatment with azathioprine with eventual clearing of lesions.

DISCUSSION

Cryoglobulins are produced by the clonal expansion of B cells, secondary to either lymphoproliferative disorders or persistent immune stimulation triggered by chronic infections or autoimmune diseases [8]. Cryoglobulinemic disease was described in 1966 by Meltzer and colleagues, who reported 29 patients with cryoglobulins and a common clinical presentation (purpura, arthralgia, and weakness), accompanied by organ dysfunction and raised serum concentrations of rheumatoid factor [9].

Three types of cryoglobulin are recognized according to type of immunoglobulins and clonality. Type I consists of monoclonal immunoglobulin. Type II and III, also called mixed cryoglobulinemias, consist of a mixture of IgM with rheumatoid factor activity and IgG components. Immunofixation of the redissolved cryoprecipitate, if feasible, allows for identification of the type of cryoglobulin [2]. In our case, information regarding the composition of cryoglobulins was not possible.

While type I cryoglobulinemia has been described in association with lymphoproliferative disorders, type II and III cryoglobulinemias have been associated mostly with infectious etiologies and autoimmune disorders [2]. In a study conducted including 443 patients with positive cryoglobulins in serum, 24% had an underlying autoimmune disease, among which 0.5% of patients presented with RA [3]. A thorough work up was performed in our patient and was found remarkable for strongly positive anti-citrullinated peptide, positive rheumatic factor levels, and positive ANA screening (1:160, homogenous).

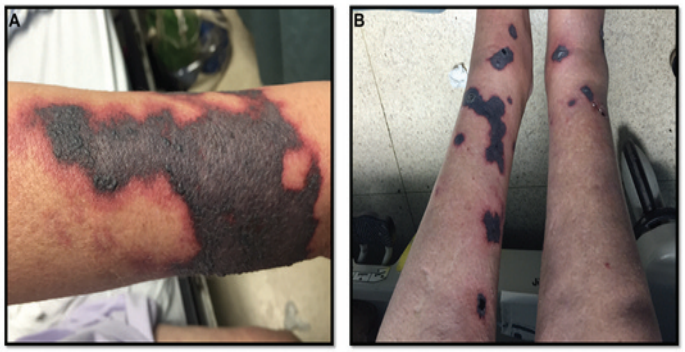

Figure 1. Multiple purpuric macules and patches with erythematous borders and central necrosis in: (A) forearm and (B) lower extremities.

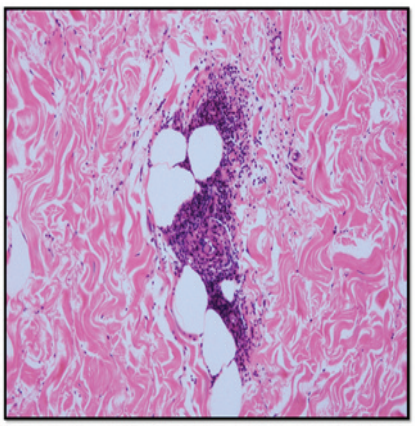

Figure 2. Histopathologic representations of leukocytoclastic vasculitis with thrombosis of small vessels.

Neoplastic disorders have been associated with vasculopathic syndromes. These paraneoplastic vasculities affect most commonly small vessels presenting as leukocytoclastic vasculitis [6]. Nozawa et al., reported a case of a 63-year-old female presenting with cutaneous vasculitis caused by hypereosinophilic syndrome and mixed cryoglubulinemia, subsequently diagnosed with diffuse large B- cell lymphoma and early gastric cancer [10]. Similarly, Solans et al., described fifteen patients in whom both vasculitis and solid tumors occurred within the same 12 months[5]. One possible explanation for this presentation is the invasion of circulating tumor cells into the vessel wall with subsequent damage to the endothelium and cross reaction between autoantibodies and tumor antigens 10. Paraneoplasltic arthritis with elevated anti-CCP has also been reported in association with lung cancer [7]. Due to its high specificity for rheumatoid arthritis (RA), a positive result may direct the physician towards the diagnosis of RA without considering other potential entities. Strongly positive anti-CCP observed in our patient put into question the possibility of pre-clinical rheumatoid arthritis, an asymptomatic phase in the RA development. Although thorax and abdominopelvic imaging studies failed to show any evidence of a malignancy, our patient was informed about a possible risk for developing cancer in the future. Consequently, she was oriented to perform regularly screening studies and to maintain a high index of suspicion in case of developing alarming symptoms.

Since characteristic skin lesions can embrace a wide variety of etiologies, they often require a systematic approach to make the appropriate diagnosis. RP presents as reticular or branching purpuric lesions. Lesions with underlying vasculitis are commonly tender and depict ongoing inflammation. A skin biopsy is always needed to distinguish inflammatory from non-inflammatory lesions. Moreover, histopathologic findings are crucial in giving direction to the diagnostic evaluation [1].

Leukocytoclastic vasculitis is the hallmark of mixed cryoglobulinemia. In patients with histopathologic findings consistent with small and medium vessel vasculitis, initial work up including complete blood count, urine analysis, rheumatoid factor, ANA, and cryoglobulins is critical to guide our diagnostic algorithm. In the presented case, cryoglobulinemia was high in our differential diagnosis given our patient's clinical and histopathological findings.

Upon re-testing during hospitalization, cryoglobulins were found to be positive, reflecting that repeated screening may be necessary to avoid false negative results owing to improper processing of the blood samples. The diagnosis of cryoglobulinemia requires demonstration of the presence of cryoglobulins in serum. Sampling collection and handling are crucial for their detection. Blood samples should be collected in pre-warmed syringes and tubes, transported, clotted, and centrifuged at 37–40°C, ensuring that the temperature never falls below 37°C [2]. If a high degree of suspicion of disease exists, cryoglobulins should be assayed serially[11].

In addition to treating the underlying cause when possible, there are three broad approaches in the treatment of cryoglobulinemia: conventional immunosuppression, antiviral treatments, and biological therapy. The severity of organ involvement and how many are affected are very important when planning therapeutic approaches. High dose steroids and cyclophosphamide remain the best choice to control severe disease and can help to reverse the course of disease, if used judiciously as a bridge to antiviral or biological agents[12]. In the presented case, the patient was experiencing progressive worsening skin lesions, reason why steroid treatment was initially started. However, after bridging therapy to azathioprine, the skin lesions totally resolved.

CONCLUSION

This case illustrates an apparent clinical association between suspected paraneoplastic vasculitis, cryoglobulinemic syndrome and retiform purpura. The histopathologic findings and absence of a clear etiology portrays the possibility of the development of a malignancy in the future, putting into question whether cryoglobulinemic syndrome was in fact a paraneoplastic syndrome. If this were the case, further studies are warranted in this direction to elucidate and shed light over this possible clinical association. Additionally, we highlight the importance of effective diagnostic re-testing when highly clinical suspicion exists, to avoid complicated laboratory evaluations, multiple specialist referrals, and delay of treatment.

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DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Value-based Healthcare: Por un enfoque en el paciente y sus necesidades

En varios sistemas de salud alrededor del mundo, la desigualdad en el acceso a los servicios va de la mano con el alto costo económico que representa para sus pacientes. Solo en Estados Unidos se estima que el gasto por persona es de $55 mil cada año; mientras que países como Alemania, Canadá y Japón gastan menos de $33 mil. Como si fuera poco, este alto costo no garantiza un estado óptimo de salud: la expectativa de vida en Estados Unidos es de 79 años, mientras en Japón, por ejemplo, es de 82.3 gastando apenas un 6% de su producto interno bruto (PIB).

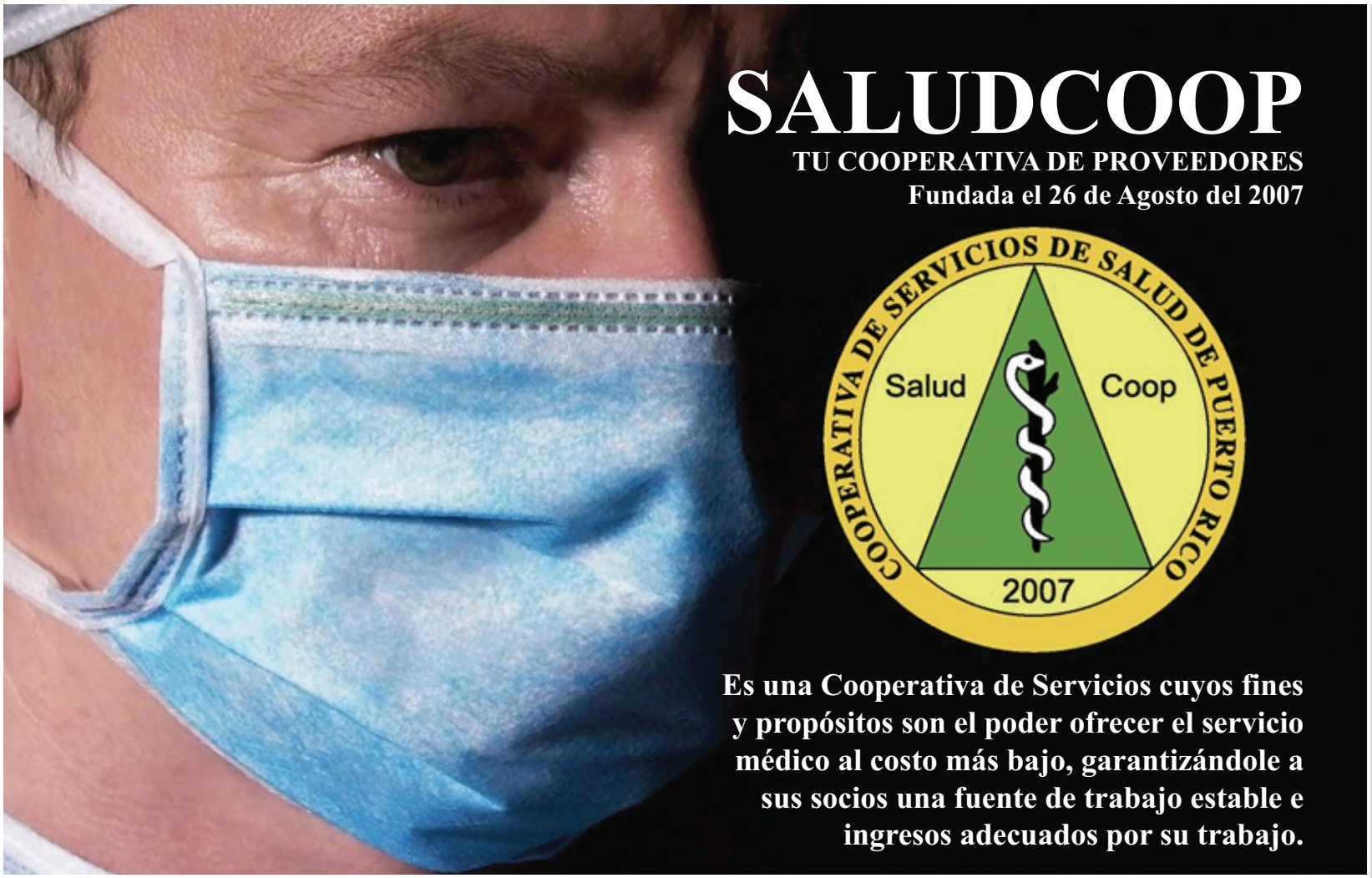
A esta realidad, se añaden las tareas administrativas que ejercen presión y consumen el tiempo los doctores justo a sus pacientes, influyendo, irremediablemente, en la calidad del servicio que se les brinda a estos. Menos tiempo para atender sus necesidades, en adición a la falta de sincronización entre tecnologías y especialistas, puede derivar en diagnósticos errados o incompletos, lo que pone en riesgo la salud y la vida misma de los pacientes.

En Redefining Health Care, un texto escrito por Michael Portberg y Elizabeth Teisberg en 2006, se menciona el concepto de relacionar los resultados de tratamiento médico con los costos de estos; es decir, proveer beneficios al paciente a la vez que se les atiende desde un enfoque holístico y preventivo, y se realizan cambios en las entidades que se encargan de proveerles servicios de salud. Con esto, se pretende garantizar que se preste particular atención al bienestar general de los pacientes, sin olvidar que también los proveedores serían incentivados por mejorar la calidad del cuidado que brindan.

De hecho, a diferencia de un cuidado de salud basado en volumen, que es como actualmente opera buen número de los sistemas alrededor del mundo, el value-based healthcare pretende rendir cuentas sobre el estado de los pacientes; proveer más opciones para ellos, lo que reduciría la desigualdad en el acceso a la salud; se proveería mejor cuidado a los pacientes con condiciones crónicas, debido a una alta interoperabilidad y comunicación entre especialistas y tecnologías; y se reducirían costos, tanto para pacientes como para las prácticas médicas.
Es alentador saber que en Latinoamérica ya se ha comenzado a explorar la idea, puesto que Colombia es uno de los países que mira al modelo de value-based healthcare en la actualidad. Darle un vistazo al escenario en Puerto Rico es crucial; especialmente considerando el estado de salud de los puertorriqueños y los retos que enfrenta nuestro sistema tras eventos como el huracán María.

Hay que tener presente que se han generado varios debates en lo que respecta a la definición de value-based healthcare; sin embargo, esto debe servir como punto de reflexión puesto que, sin importar el interés de los diferentes sectores que tienen que involucrarse al momento de proveer servicios de salud a la población, el norte debe ser uno: garantizar que la calidad de vida de los pacientes mejora constantemente mediante la optimización de servicios. Esto está sucediendo en este momento: cada vez son más las innovaciones tecnológicas, industrias e instituciones educativas que forman a profesionales de la salud enfocados en el valor y en obtener resultados de primera.

Finalmente, el value-based healthcare guarda grandes promesas para el sistema de salud, aquí en Puerto Rico y donde sea. A fin de cuentas, un sistema que mejora los procesos del cuidado de la salud y la calidad de vida de los pacientes no solo debe ser tomado en cuenta, sino puesto como una de las más grandes prioridades en cualquier país.



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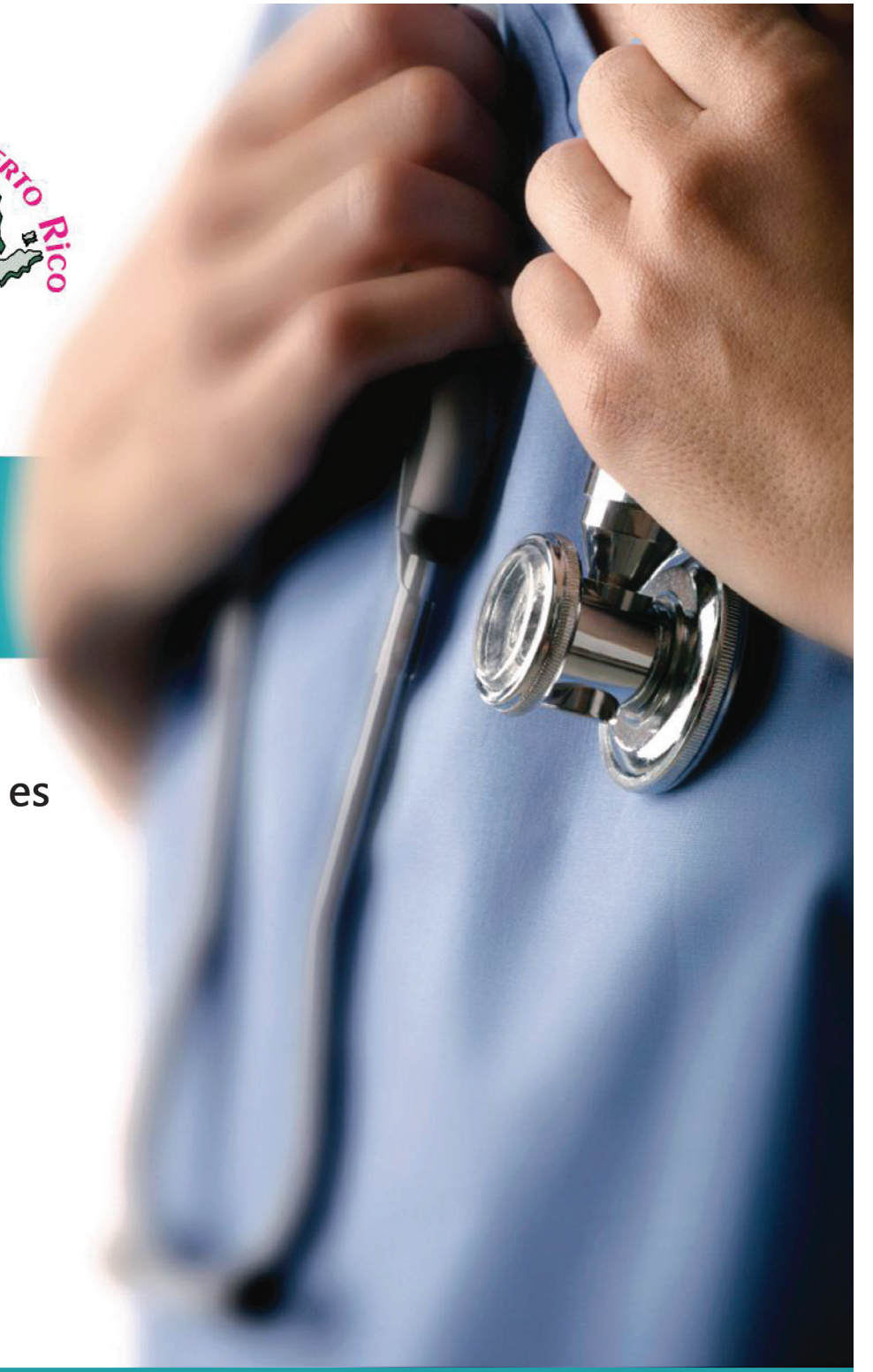

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