

REPORT

Metformin potential in predisposing arthralgia, type II cross reactivity secondary to group A *streptococcus* infection & other comorbidities in treating PCOS

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Abstract: One of the most common endocrinological disorder affecting women in adolescence is Polycystic Ovarian Syndrome (PCOS). Women suffering from PCOS diagnosed with follicles in ovaries show enlarged reproductive organs with small filled follicles. Unusual bleeding, prolonged menstruation, unwanted hair growth, accumulation of fat and acne are the most common problems experienced by adolescents with PCOS. Nowadays, PCOS is treated successfully with the oral antidiabetic drug, metformin and hormone replacement therapy. Its off-label use is still controversial with unknown mechanisms due to patient risk versus benefit hypothesis by practitioners as they successfully treat PCOS in adolescents with metformin. But in few reported cases metformin has potential to induce back pain and swollen joints less frequently with rare cases of behavior alteration. Penicillin belongs to the beta-lactam antibiotics and is most commonly used to treat rheumatic fever although it has potential to cause allergic reactions affecting 10% of patients who exhibit IgE-mediated immunological reactions. Here, we present a case of a female diagnosed with PCOS who after treatment with metformin for more than two years, reported with hyperuricemia, migraine, neurological pain, severe joint and knee pains on shoulders and legs, and rheumatic fever. After treatment with benzathine benzyl penicillin for rheumatic fever, the patient also exhibited Type IV delayed hypersensitivity reaction.

Keywords: Benzyl penicillin, metformin, PCOS, rheumatic fever.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a group of endocrinological, gynecological disorder characterized by infertility, irregular menstruation, hypergonadism, body hair growth and acne which affects about 5-10% of adolescents. Infertility is major complication, inferior to myocardial risk, associated with PCOS like others metabolic syndrome (Tehrani and Behboudi-Gandevani 2015; McCartney and Marshall 2016). Various literature reviews and meta-analyses proved efficacy of metformin in treating PCOS successful (Lord, Flight *et al.* 2003; Nandi, Chen *et al.* 2014; Azziz, Carmina *et al.* 2016). Rheumatic fever is an acute fever characterized by fever, anorexia, lethargy and joint pains. Arthritis occurs in approximately 75% of patients and other features include skin rashes, carditis and neurological features. The treatment of choice is Penicillin (either oral penicillin V or injectable benzathine penicillin) (Irlam, Mayosi *et al.* 2013). Penicillin is also given as a prophylaxis. The recommended period of prophylaxis depends on the number of previous attacks. For penicillin-allergic individuals, acceptable alternatives include first generation cephalosporins, clindamycin, or various oral macrolides or azalides. In controlled studies that have

been considered, the only currently recommended treatment is Penicillin to avoid initial attacks of acute rheumatic fever (Gerber, Baltimore *et al.* 2009). This acute fever is usually caused by group A streptococci infection that contains cross reactive antigen invade connective tissues and myocardial valve which affect mostly young and growing children. It is highly prevalent in south Asia and Africa (Wilson 2007; Seckeler and Hoke 2011; Irlam, Mayosi *et al.* 2013).

In this case, we highlighted a case of PCOS female patient receiving metformin treatment and experienced joint swollen, hyperuricemia, migraine, peripheral neuropathy and rheumatic fever after metformin treatment. Patient disease state aggravated after receiving benzyl penicillin for rheumatic fever and experienced type IV hypersensitivity reaction very frequently.

Case presentation

A 22 year old Pakistani young girl presented in clinic with severe joint pains i.e. knees, shoulders and leg joints. Patient had past complaint of rheumatic fever treated with benzathine benzyl penicillin 6 days ago. Patient had also reported complaints of penicillin-induced Type IV delayed hypersensitivity reaction, presenting rashes all over the body.

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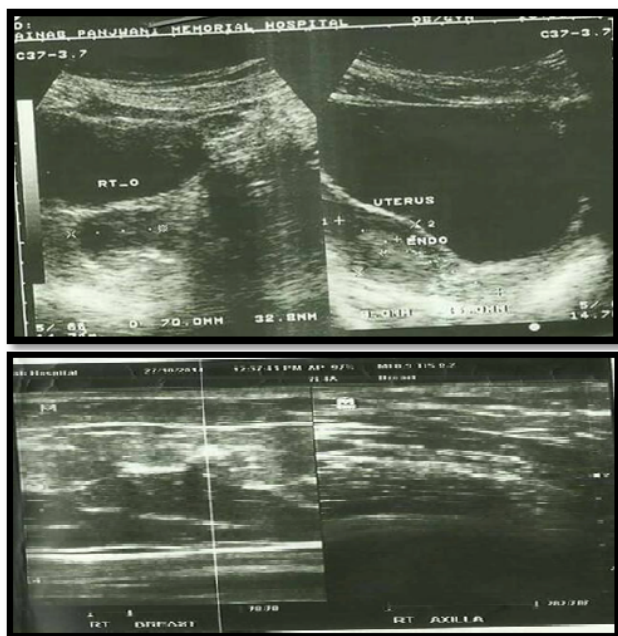


Fig. 1: (A & B) abdominal ultrasound of right and left ovaries showing multiple follicles

The past medical history revealed that she had an equivalent rate of pain attack 4-5 months prior. The pain was treated by self-medication. Her medication history revealed that she was not taking any medicines other than the periodic pain-relieving medication for cerebral pain. Her social history revealed that she was not a smoker or a shopper of liquor. She had co-morbid disease states like PCOS (fig. 1), high level of uric acid, sinusitis, breast pain (fig. 2). Patient's past medical antiquity from onset of puberty to end of adolescence showed she was healthy, fit and fine before PCOS diagnosis. She was very active in athletics with no serious medical complications. Before two years ago she suddenly developed unusual and disturbed menstrual cycle and weight gain from 40kg to 65kg. Upon gynecological recommendation, after ultrasound reports, she was diagnosed with Polycystic ovarian syndrome (PCOS). She started treatment with metformin at a recommended dosage of 500mg B.I.D for 6 months. After 4 months, this patient on metformin experienced undesired effects such as: severe body pain (particularly on joints and legs), breast tenderness and pain in axilla, hyperuricemia with a mean value 6.8mg/dl (laboratory standard normal: 2.4-5.7mg/dl), frequent throat infection (positive culture with group A streptococcal pyrogens), cluster of headache, palpitation and mood alteration. Patient received multiple analgesics i.e. Ibuprofen 600mg/day, mefenamic acid 500mg Q.I.D, and acetaminophen 50mg/kg/day as pain reliever including amoxicillin plus clavulanic acid 40mg/kg, Allopurinol 100mg/day, ranitidine 150mg B.I.D, oral betamethasone 0.5mg TID for gargles of infected throat. After careful consideration, the physician recommended confirmatory diagnostic test for rheumatic fever based on

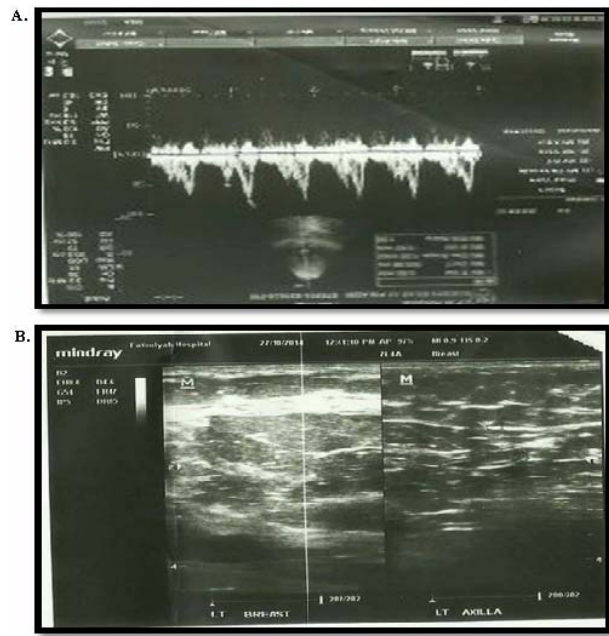


Fig. 2: (A & B) ultrasound of left and right breast and axilla with no abnormal function.

minor diagnostic criteria of arthralgia, myalgia, fever and positive culture of streptococcus pyrogens. Patient ran blood test of Antistreptolysin O titre (ASOT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and Rhesus (Rh) variable. All tests showed variable results with minor elevation of CRP value 1.5mg/liter in blood (normal laboratory standard ≤ 1.0 mg/liter), Positive ASOT test with a mean value 425IU/ml (normal laboratory standard ≤ 200 IU/ml), rheumatoid factor 4.8IU/mL (normal < 14 IU/ml). After the test it was certain and the specialist gave her treatment with benzathine benzyl penicillin 1.2million units/month IM diluted in 10ml water for injection. She always experienced severe painful procedure with palpitation (heart rate: 150 beats/minute). For confirmation, electrocardiography test was performed (fig. 3) to ensure myocardial function. After the association, the physician kept the patient under observation for 6 hours, yet there was no unfavorably susceptible response aside from intoxication. After 1 week, there was a high swelling at the site of infusion with blue shading. This was an undesirable response with pain, skin rash with sloughing and itching. One reaction was additionally observed with benzathine benzyl penicillin i.e., high fever. Physician treated it as a usual post drug response from penicillin with intravenous injection of Pheniramine maleate 20mg, cyanocobalamin 100mg/day for neurological pain with sudden withdrawal metformin therapy.

DISCUSSION

This was the case of a 22-year-old female patient who had no active complaint of type II mediated immune reaction

(RF), hyperuricemia, neurological pain, myalgia, migraine, frequent tonsillitis and throat infection before 2 years ago when she was diagnosed with PCOS. She was very active athlete before PCOS diagnosis. After irregular menstruation and obesity physician prescribed her metformin after multiple cyst confirmatory test by ultrasound. After continuous use of metformin, she suddenly developed undesirable effects diagnosed with marked uric acid level, sinusitis, breast tenderness, uncontrolled bleeding with reducing number of follicles in ultrasound. Physician did not withdraw metformin immediately but just treated all these symptoms by traditional medication. After 5 months, the patient was diagnosed with rheumatic fever on the basis of the diagnostic criteria by Jones (Roberts, Colquhoun *et al.* 2013; Burke and Chang 2014) and laboratory values which indicated marked ASOT level and rheumatoid factor. Rheumatic fever is acute fever elicited with susceptible strains of Group A streptococci which possess antigen that cross-react with human connective tissue, particularly a heart valve glycoprotein. The condition usually affects children and young adults, and there is a familial variation susceptibility (Gerber, Baltimore *et al.* 2009).

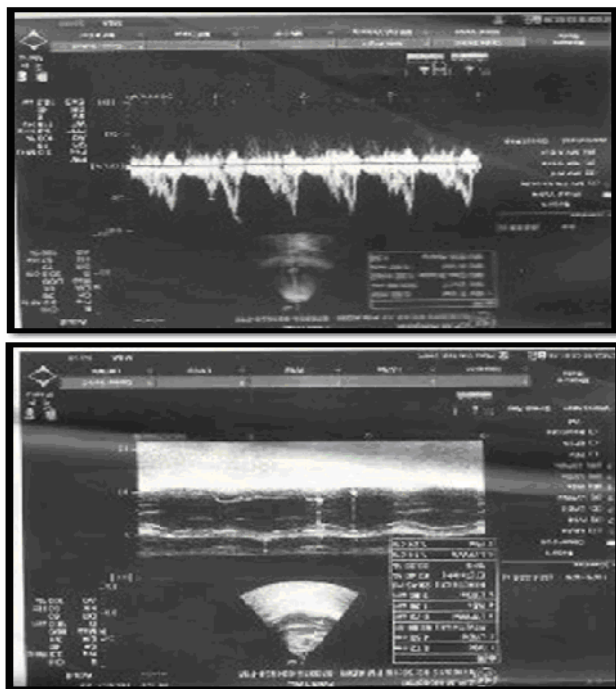


Fig. 3: (A & B) Electrocardiography shows normal ventricle function.

Conventionally, rheumatic fever is treated by benzathine benzyl penicillin which is very effective in control of Group A streptococcal pyrogens but 1 in 10 individuals experience hypersensitivity reaction (Chang, Mahmood *et al.* 2012; Macy and Contreras 2014). The patient also experienced type IV delayed hypersensitivity reaction

with intense itching and rashes all over the body after 6 days of intramuscular injection. After this antigen antibody-mediated immune response, the physician changed the therapy of the patient to oral penicillin Co-amoxiclav and the allergic response treated by Pheniramine maleate and different oral non-sedative anti-allergic drugs like fexofenadine and levocetirizin. Postponed excessive touchiness or Type IV responses can likewise happen with introduction to penicillin. Lymphocytes and macrophages are accepted to intercede these responses, which can occur in various ways. Contact dermatitis is also most frequent manifestation attributed to penicillin (Pyle and Rattner 1944; Gimenez-Arnau, Maurer *et al.* 2010).

Intense interstitial nephritis can happen with any penicillin yet it is most usually connected with methicillin and it is agreed to be caused by a Type IV response. Renal inadequacy can happen, alongside hematuria, eosinophilia and proteinuria. This impact is typically reversible upon medication cessation (Chang, Mahmood *et al.* 2012; Macy and Ngor 2013; Picard, Bégin *et al.* 2013). In spite of the fact that sensitivity can happen at any age, patients between 20-49 years are at higher risk for hypersensitivity Responses may be more successive and serious with parenteral plans of medication. Re-Exposure of penicillin might trigger anaphylactic reactions, approximately 60% of patient allergic to patient will must experience upon second presentation (Bhattacharya 2010).

It might, on the other hand, be hard to observe the 15% of patients who will be sure to have an unfavorably susceptible response upon re-challenge without skin testing. Customarily, atopic people are more inclined to penicillin hypersensitivity. Family history of hypersensitivity is additionally, not a danger component. At the point when penicillin G is utilized intramuscularly, <1% of patients will encounter a procaine response comprising of dazedness, sound-related, visual, and/or taste unsettling influences, neuromuscular jerking, and an apprehension of up and coming demise. This response has been connected with measurements of 4.8 million units and commonly keeps going up to 10 minutes (Khan and Solensky 2010).

CONCLUSION

In this case, the patient's therapy was changed to oral penicillin with withdrawal of metformin therapy, and after 3 months the patient had a gradual decline in complaints of myalgia, there was mood alertness, reduced hyperuricemia, normal CRP value and improved ASOT and RF scores. All these evidences clearly reflect metformin potential in the induction of joint pains, hyperuricemia, headache, mood alteration and other immune mediated type II cross reactivity secondary to

group A streptococcal pyrogens causing pharyngitis, tonsillitis with other co-morbidities in susceptible individuals.

REFERENCES

- Azziz R, Carmina E, Chen Z, Dunaif A, Laven JS, Legro RS, Lizneva D, Natterson-Horowitz B, Teede HJ and Yildiz BO (2016). Polycystic ovary syndrome. *Nat. Rev. Dis. Primers*, **2**: 16057-16057.
- Bhattacharya S (2010). The facts about penicillin allergy: a review. *J. Adv. Pharm. Technol. Res.*, **1**(1): 11.
- Burke RJ and C Chang (2014). Diagnostic criteria of acute rheumatic fever. *Autoimmun. Rev.*, **13**(4): 503-507.
- Chang C, Mahmood MM, Teuber SS and Gershwin ME (2012). Overview of penicillin allergy. *Clin. Rev. Allergy Immunol.*, **43**(1-2):84-97
- Gerber MA, Baltimore RS, Eaton CB, Gewitz M, Rowley AH, Shulman ST and Taubert KA. (2009). Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. *Circulation.*, **119**(11): 1541-1551.
- Jimenez-Arnau A¹, Maurer M, De La Cuadra J, Maibach H (2010). Immediate contact skin reactions: An update of Contact Urticaria, Contact Urticaria Syndrome and Protein Contact Dermatitis: Never Ending Story. *Eur. J. Dermatol.*, **20**(5): 552-562.
- Irlam J, Mayosi BM, Engel M and Gaziano TA (2013). Primary prevention of acute rheumatic fever and rheumatic heart disease with penicillin in south african children with pharyngitis. *Circ. Cardiovasc. Qual. Outcomes*, **6**(3): 343-351.
- Khan DA and R Solensky (2010). Drug allergy. *J. Allergy Clin. Immunol.*, **125**(2): S126-S137. e121.
- Lord JM and IH Flight and Jorman RJ (2003). Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ.*, **327**(7421): 951.
- Macy E and R Contreras (2014). Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. *J. Allergy Clin. Immunol.*, **133**(3): 790-796.
- Macy E and EW Ngor (2013). Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin and oral amoxicillin. *J. Allergy Clin. Immunol. Pract.*, **1**(3): 258-263.
- McCartney CR and JC Marshall (2016). Polycystic ovary syndrome. *N. Engl. J. Med.*, **375**(1): 54-64.
- Nandi A and Z Chen *et al.* (2014). Polycystic ovary syndrome. *Endocrinol. Metab. Clin. North Am.*, **43**(1): 123-147.
- Picard M, Bégin P, Bouchard H, Cloutier J, Lacombe-Barrios J, Paradis J, Des Roches A, Laufer B and Paradis L (2013). Treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital. *J. Allergy Clin. Immunol. Pract.*, **1**(3): 252-257.
- Pyle H and H Rattner (1944). Contact dermatitis from penicillin. *JAMA*, **125**(13): 903-903.
- Roberts K, Colquhoun S, Steer A, Reményi B and Carapetis J (2013). Screening for rheumatic heart disease: Current approaches and controversies. *Nat. Rev. Cardiol.*, **10**(1): 49-58.
- Seckeler MD and TR Hoke (2011). The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. *Clin. Epidemiol.*, **3**: 67.
- Tehrani FR and S Behboudi-Gandevani (2015). Polycystic ovary syndrome. *Contemporary Gynecologic Practice, InTech.* <http://dx.doi.org/10.5772/59591>
- Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, Bolger A, Cabell CH, Takahashi M, Baltimore RS, Newburger JW, Strom BL, Tani LY, Gerber M, Bonow RO, Pallasch T, Shulman ST, Rowley AH, Burns JC, Ferrieri P, Gardner T, Goff D and Durack DT (2007). Prevention of infective endocarditis guidelines from the American Heart Association. *J. Am. Dent. Assoc.*, **138**(6): 747-760.