

PASH syndrome with Etanercept treatment, a case report.

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ABSTRACT:

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PASH syndrome is a rare condition that consists of pyoderma gangrenosum (PG), acne and suppurative hidradenitis. It is described as an auto-inflammatory disorder in the same spectrum of PAPA syndrome (pyoderma, acne and pyogenic arthritis). The mainstay of the treatments are immunosuppressive drugs. Tumor necrosis factor α (TNF- α) inhibitors have been reported some benefits in patients with PASH syndrome. We present the case of a 20-year-old man who developed severe acne, ulcers, abscess formations and draining sinuses on the face, neck, trunk, intertriginous areas and extremities. He was ultimate diagnosed with concurrent PASH syndrome. The diseases remitted in response to treatment with etanercept.

Key words : PASH syndrome, pyoderma gangrenosum

บทคัดย่อ:

กาญจนา เหลืองรังษิยากุล กอบกุล อุณหโชค ชูติกา ศรีสุทธิยากร รายงานผู้ป่วย PASH SYNDROME ที่รักษาด้วย ETANERCEPT วารสารโรคผิวหนัง 2559; 32: 205-211.

แผนกโรคผิวหนัง กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า

PASH syndrome เป็นกลุ่มโรคที่พบได้ไม่บ่อย ลักษณะทางคลินิกประกอบด้วย pyoderma gangrenosum (PG), acne และ suppurative hidradenitis PASH syndrome จัดเป็นกลุ่มโรคที่มีการอักเสบบริเวณผิวหนัง เช่นเดียวกับโรคในกลุ่ม PAPA syndrome การรักษาหลักคือการใช้ยาในกลุ่มกดภูมิคุ้มกัน รวมถึงยา กลุ่มต้านการทำงานของ TNF- α ซึ่งมีการรายงานว่าให้ผลการรักษาที่ดีในผู้ป่วยกลุ่ม PASH syndrome บทความนี้เป็นการรายงานผู้ป่วยชายอายุ 20 ปี มาด้วยมีสิวกอักเสบรุนแรง, แผล, ฝี บริเวณใบหน้า, คอ, ลำตัว, ซอกพับและแขนขา 2 ข้าง วินิจฉัย PASH syndrome ได้รับการรักษาด้วย etanercept ผู้ป่วยตอบสนองต่อการรักษาได้ดี เป็นที่น่าพอใจ

คำสำคัญ: กลุ่มโรค PASH, Pyoderma gangrenosum

Case report

A 20-year-old Thai man presented with severe acne, ulcers, abscess formation and draining sinuses on the face, neck, trunk, intertriginous areas and extremities for 2 years. He had no systemic symptom and denied any history of arthritis or bowel habit change. No other members in his family obtained the similar symptoms. The patient had been treated with isotretinoin, prednisolone and cyclosporine without improvement.

The physical examinations showed multiple erythematous papules, tender cystic nodules and pustules with multiple hypertrophic scars, multiple ulcers and erosions with yellowish crust on the face, neck, trunk, axillae, groins and extremities. No arthritis or arthralgia was noted.

The skin biopsy from the lesion showed pseudoepitheliomatous hyperplasia,

intraepidermal neutrophilic abscesses and sinus tracts formation. Granulomas with neutrophils infiltration were found in the dermis and perifollicular areas. The special stains with PAS, GMS, AFB, modified AFB, tissue culture for fungus, bacteria and tissue PCR for *Mycobacterium spp.* were all negative. Further investigations including CBC, renal function and liver function tests and chest radiography were normal. The serum study for anti-HIV, anti-HCV and HBsAg were also negative.

The patient was diagnosed as PASH syndrome and the treatment was started with etanercept 50 mg twice weekly, combined with prednisolone 40 mg/day. After 5 months of the treatment, the clinical was improved.



Figure 1,2 Multiple erosions and scars on cheeks, neck and upper back



Figure 3 Five months after treatment with etanercept 50 mg weekly combined with prednisolone 40 mg/day

Discussion:

PASH syndrome is a recently reported a rare condition that consists of a triad of pyoderma gangrenosum (PG), acne and suppurative hidradenitis. It is described as an auto-inflammatory disorder in the same spectrum of PAPA syndrome (pyoderma, acne and pyogenic arthritis). This spectrum also included the new entities; PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne, hidradenitis suppurativa, PsAPASH syndrome (psoriastic arthritis, pyoderma gangrenosum, acne and hidradenitis suppurativa) and PASS syndrome (pyoderma gangrenosum, acne conglobata, suppurative hidradenitis and axial spondyloarthritis).^{1,2}

PASH syndrome was first described by Braun-Falco M, et al in the year 2012.^{3,4} It has unknown genetic basis. Polymorphic profiles of genetic mutations were detected in PASH syndrome.^{4,5,6} Unlike PAPA syndrome, which is an autosomal dominant, caused by mutation in involving the proline-serine-threonine-phosphatase-interacting protein 1 (PSTPIP1) gene.^{4,7} PSTPIP1 bind to pyrin which are the parts of inflammasomes in granulocytes and monocytes. The mutation in PSTPIP1 causes loss of inhibitory effect of pyrin which increase the inflammatory processes via IL-1b production.^{4,5}

โฆษณา 4 สัปดาห์

The reported genetic abnormalities in PASH included the increased number of CCTG microsatellite repeats in the PSTPIP1, nicastrin gene mutation and also the genes involved in group of autoinflammatory diseases (NLRP3, IL1RN, MEFV, NOD2 and PSMB8).^{4,5,6,8} All of the genes were involved in the inflammatory cascade, result in increased IL-1b production and hyperactivated innate inflammatory responses.⁸

The mean age at the time of diagnosis has been reported as 32.2 years(range 16-45 years).^{5,7} The clinical presentations consist of severe acnes, usually on face, hydradenitis suppurativa at intertriginous areas and pyoderma gangrenosum, usually on trunk and extremities.^{5,7}

The associated of PASH with morbid obesity, ulcerative colitis and Crohn's disease have been reported, but not strong.^{5,7} Different from pyoderma gangrenosum itself which has numerous coexisting conditions between 50-70%.⁴ In PG, the most common associations are inflammatory bowel diseases, arthritis and hematologic diseases.⁹

Additionally, the increase CCTG motif in PSTPIP1 gene has been found associated with the aseptic abscess syndrome which 20% found cutaneous abscessed and neutrophilic dermatoses.^{4,10} As some cases of PASH syndrome had the same mutation. Nevertheless, no report of PASH with visceral abscessed was found. The possible explanation is the different of location

of mutation within PSTPIP1 gene influence the organ predilection.⁴

In this case, the diagnosis was made mainly by the clinical presentations. Histopathology in this case cannot help for diagnosis, but can use as a tool to rule out other accompanied infectious diseases. Our patient lacked the symptom of bowel habit change and stool occult blood was negative. We desire the further work up with colonoscopy is not necessary according to the weak association with inflammatory bowel diseases from the previous reports.⁵

The treatments in this group of auto-inflammatory diseases are difficult. Many treatment modalities were reported with variable results.⁸ The main therapeutic agents were immunosuppressive drugs, included systemic steroids, cyclosporine and anti-inflammatory agents such as dapsone.⁸ Surgical treatment has been reported in the hidradenitis suppurativa lesions.^{3,7}

Recently, biologic agents such as TNF- α inhibitors have been used with increased frequency as novel treatments for several dermatologic diseases including psoriasis, dermatomyositis, neutrophilic dermatosis, pyoderma gangrenosum, hidradenitis suppurativa and autoimmune bullous disease.^{9,11} Infliximab, adalimumab or etanercept has been used as a therapeutic agents in PASH syndrome.^{7,8}

Unfortunately, the disease had partial improvement without cure.^{4,5,7}

Adjoining with PAPA syndrome, PASH syndrome also has abnormal mechanism via IL-1b. Anti-IL -1 receptor antagonist (anakinra) is one of the drug of choice, but the results were not complete remission.^{4,7,8}

Angelo V, et al evaluated the expression of cytokines from the skin biopsy at pyoderma gangrenosum lesions in 5 patients who had a diagnosis as PASH syndrome. They found significant overexpressed of IL-1b, IL-1 receptors, TNF- α and TNF-receptors and IL-7 and IL-7 receptors compared to normal skin.⁵ This study showed the complex mechanism of inflammation in PASH syndrome. These can explain the partial response of PASH syndrome to either IL-1 receptor antagonists or anti-TNF agents.^{12,13} Therefore, combination treatments with biologic agents and immunosuppressants may be helpful.⁸

According to the unsuccessful of previous therapies with anti-inflammatory agents, retinoids and immunosuppressive agents in our case, we decided to start a biologic agent. As the IL-1 receptors antagonist is not available in Thailand. We selected anti-TNF- α , etanercept, which has lower price and easier to use compare to infliximab.

Etanercept 50 mg subcutaneously once a week was started. After 2 weeks of therapy, the

lesions had partial improvement. We increased the dose of etanercept to 50 mg twice weekly, as the same regimen as in PG and psoriasis or psoriatic arthritis.^{11,14} After 2 months of treatment, the clinical was marked improvement and prednisolone was tapered to lower than 20 mg per day. No side effect or complication was found in this patient.

In conclusion, we reported PASH syndrome with good response to etanercept. Although there is no cure, the treatment can improve the patient's quality of life. As the unknown genetic abnormalities and polymorphic profiles of genetic mutations were presented, the treatment results were different individually. Treatment options were depended on patient's condition and physician's experience. Genetic testing may help the physician to selected agents directly target the abnormalities.

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