中文題目：腹膜透析患者德貝里菌屬腹膜炎及 methotrexate 相關性全血細胞減少症

英文題目：Debaryomyces etchellsii peritonitis and methotrexate-related pancytopenia in a patient under peritoneal dialysis

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Background: This 64-year-old lady under regular peritoneal dialysis was admitted for unusual presentation of peritoneal dialysis-peritonitis and pancytopenia after taking low dose methotrexate for bullous pemphigoid. Methotrexate has high volume of distribution and is a hydrophilic agent. 90% of methotrexate is excreted unchanged in the urine. It can be toxic in end stage renal disease (ESRD) patients even at low doses with the side effect of bone marrow suppression. Hereby, we presented a peritoneal dialysis patient with low-dose methotrexate-induced pancytopenia and ***Debaryomyces etchellsii***-related fungal peritonitis.

Case report: This 64-year-old lady has been under peritoneal dialysis for 9 years due to end stage renal disease, caused by urinary tract tuberculosis 15 years ago. 4 months prior to admission, she experienced bullous eruption over the body and diagnosed as bullous pemphigoid under the pathological finding of subepidermal blister with negative immunofluorosence stain. She was treated with antihistamine, prednisolone and topical agent. One month prior, methotrexate 5 mg per week was added for her progressive skin lesions with folic acid replacement. She developed painful oral ulcers after taking a total cumulative dose of 10 mg of methotrexate 2 week before admission. At the same time, she passed loose whitish stool for many times with mucous content. Diffuse dull abdominal pain with a pain score of 5-6 in nature was complained. She presented to our hospital with ill-looking appearance and diffuse oral ulcers. Physical examination showed diffuse abdominal pain without rebounding tenderness. Peritoneal dialysis fluid showed clear dialysate (Table 1). Laboratory data showed pancytopenia with high inflammatory markers (Table 2). Abdominal computed tomography revealed mild some jejunum wall thickening at left upper abdomen and mild ascites. 50 white blood cells per high power field was noted on peritoneal dialysate while only 540 of white blood cells per cumm in peripheral blood. Empirical antibiotic with Piperacillin/Tazobactam, Gentamicin and Micafungin were given. Parenteral nutrition was given for mucositis. Continuous renal replacement therapy and leucovorin rescue therapy were prescribed for methotrexate intoxication. 2 days after admission, dialysate was found to be cloudy and pus-like discharge with 2385 white blood cells per high power field. Dialysate smear showed yeast and culture disclosed Debaryomyces etchellsii. Peritoneal dialysis catheter was removed immediately with peritoneal lavage and drainage under Micafungin and Amphotericin B treatment. At the same time, serum and dialysate methotrexate level were closely monitored and all under safety level. She was intubated for severe sepsis-related acute respiratory distress syndrome on 6th day of admission. After one month of combined antifungal treatment, Debaryomyces etchellsii was

successfully eliminated. After 5 weeks of hospital stay, the patient passed away due to opportunistic infection with multiorgan failure.

Discussion: Debaryomyces etchellsii is a white, dull to glistening and butyrous, moderately well-branched pseudohyphae with formation of a few blastoconidia. Majority of this pathogen is isolated from pickle fermentations showing its tolerance to high salt substrates with low pH. Till now, clinical importance is unknown and in 1959, one strain was isolated from human feces.

Methotrexate (MTX; molecular weight, 454.4 kDa), an antimetabolite of folic acid, is approximately 50% albumin bound in plasma and up to 90% of the absorbed amount is excreted unchanged in the urine within 48 hours, mostly within the first 8 hours through glomerular filtration and active tubular secretion with normal kidney function. Though it is a mainstay treatment for autoimmune disease, severe toxicity can occur with impaired renal function due to delayed elimination and accumulation.[1] Side effects of MTX include pancytopenia, liver toxicity and pulmonary toxicity. Risk factors for severe bone marrow toxicity include impaired renal function, advanced age, diabetes mellitus, folic acid deficiency, hypoalbuminemia, concurrent use of nonsteroidal anti-inflammatory drugs or proton-pump-inhibitors.[2] As the main route of MTX excretion is urine, renal impairment is the single most important risk factor for methotrexate-induced pancytopenia despite the putative idiosyncratic nature in other cases.[3]

Low dose MTX-related-toxicity has been described mainly in case reports. It can be life-threatening, mainly due to myelosuppression and there is no rationale for therapeutic drug monitoring regarding low dose toxicity.[4] Following absorption, regardless of MTX dose, 10% of MTX is converted to 7-hydroxymethotrexate which together with MTX are excreted by the kidneys. The serum concentrations are undetectable 24 hours following administration. Once entering the cells, MTX and 7-hydroxymethotrexate are metabolized to polyglutamate derivatives (GluMTX) which are stored in the tissue. The half-life of GluMTX studied in RBCs demonstrated a median elimination half-life of 1-4 weeks. Since prolonged low dose MTX toxicity may be mainly mediated by the unmeasurable intracellular polyglutamate derivatives. That is why undetectable serum MTX concentration does not guarantee no clinical toxicity. These findings may explain the unnecessary routine MTX serum concentration monitoring.[4]

Conclusion:Our patient, taking regular peritoneal dialysis (PD), presented with pancytopenia after low dose MTX treatment though the MTX serum concentration level ($0.03x10^{-9}$ umol/L) was under safety level. One recently published study showed pancytopenia with opportunistic infection with low dose MTX treatment in peritoneal dialysis (PD) patients.[5] Unlikely, our patient was infected with ***Debaryomyces etchellsii*** which was refractory to treatment and cause mortality. To our knowledge, it was the first and serious infection caused by ***Debaryomyces etchellsii.*** This unexpected unusual severe infection may be due to prolonged low dose MTX toxicity. Therefore, in patients with impaired renal function and those taking renal replacement therapy, methotrexate should be avoided even in low dose treatment.