Tubo-ovarian abscess during therapy of chronic hepatitis C with pegylated interferon and ribavirin

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Abstract

BACKGROUND: Serious infections are rare complications of standard treatment in chronic hepatitis C with pegylated interferon alpha (Peg IFN) and ribavirin.
CASE: We report two cases of life-threatening tubo-ovarian abscess (TOA) in women older than 40 year of age. No casual risk factors of TOA could be identified in them. In one case septic shock and acute renal failure occured. TOA was caused by endogenic bacteria (*Porphyromonas asaccharolytica* in the first case and *Streptococcus intermedius* in the latter). Surgical treatment and interruption of IFN therapy was necessary in both cases.
CONCLUSIONS: Serious gynecological infections may have the significant negative influence on chronic hepatitis C therapy outcome. Because of the risk of TOA developing during IFN therapy gynecological care is needed in chronic hepatitis C management.

CASE REPORT

INTRODUCTION

Pegylated interferon alpha (Peg IFN alpha) combined with ribavirin (RBV) is currently the standard, highly effective treatment in chronic hepatitis C (Fried *et al.* 2002). Common adverse events of Peg IFN alpha therapy include flu-like syndrome, general malaise, fatigue, asthenia, leukopenia with neutropenia, thrombocytopenia, anaemia, injection-site reactions, depression, irritability, thyroid dysfunction. Serious infections in different localizations are rare complications during IFN therapy. Among them respiratory tract infections, bacteriemia or sepsis, endocarditis and local bacterial infections were reported. Gynecological infections, including pelvic inflammatory disease (PID), have been not described to date. PID is one of the most serious complications of sexually transmitted diseases of various etiology. It is an infection of the female upper genital tract that encompasses a broad category of diseases, including endometritis, salpingitis, salpingo-oophoritis, tubo-ovarian abscess (TOA), and pelvic peritonitis. Prompt diagnosis and treatment of this condition are critical because the complications of PID can be life- and fertility-threatening. We report

two cases of TOA during pegylated interferon alpha 2a therapy. According to our knowledge there are no reports of infections in such localization complicating this therapy.

CASE 1

Forty five-year-old woman, Caucasian, infected with hepatitis C virus (HCV), in the 32nd week of treatment with pegylated interferon alpha 2a (Peg IFN alpha 2a – Pegasys) and ribavirin (Copegus) was admitted to the surgical department because of acute lower abdominal pain with nausea and fever 38 °C lasting for 2 days. She was sexually active woman with one regular sexual partner, having 6 children, without any previous history of gynecological infections, including PID. The patient had been infected with HCV genotype 1. Infection was diagnosed 2 years before. Liver biopsy revealed inflammatory activity grade 2, fibrosis stage 2, according to modified HAI (histologic activity index) score. Moderate neutropenia was observed during first 6 weeks of therapy; the lowest count was 0.8×10^3/μl after the 5th dose of Peg IFN. On admission the patient was in bad clinical condition, without signs of peritonitis. Laboratory examinations revealed WBC 17.8×10^3/μl, hemoglobin level, platelet count, urea and creatinine levels in normal range. Abdominal ultrasound (USG) examination revealed left tubo-ovarian abscess (7 cm × 2.5 cm) and fluid visible in rectouterine (Douglas') pouch. Empiric antibiotic therapy with ciprofloxacin was conducted with minor improvement. The patient was discharged from the hospital after 3 days for further ambulatory gynecological evaluation. After next 7 days she was again admitted to the gynecological department because of acute abdominal pain, fever up to 40 °C with chills, and general malaise. Significant laboratory tests showed C-reactive protein (CRP) 212 mg/dL, white blood count 4.56×10^3/μl, hemoglobin level 9.4 g/dL. Transvaginal ultrasound examination revealed left tubo-ovarian abscess. The patient was operated on the 3rd day after admission; laparotomy was performed with peritoneal lavage and drainage with subsequent treatment with 3 antibiotics (amoxicillin/clavulanic acid, metronidazole and clindamycin). *Porphyromonas asaccharolytica* was identified in discharge from peritoneal cavity. Antibiotic sensitivity of the pathogen was not determined. The treatment of chronic hepatitis C was interrupted for three weeks and then introduced again. Three months after surgical treatment the patient was free of gynecological symptoms and without any sequelae. Eventually the therapy of chronic hepatitis C failed; virological end-of-treatment response (ETR) was not achieved.

CASE 2

Fifty seven-year-old Caucasian woman with chronic hepatitis C, treated for 3 weeks with pegylated interferon alpha-2a and ribavirin was urgently admitted to the infectious diseases department with suspicion of septic shock. Chronic hepatitis C was diagnosed 3 years before, with inflammatory activity grade 2.5, fibrosis stage 3 and steatosis grade 3 (according to modified HAI score) in liver biopsy. She was postmenopausal for 2 years, sexually inactive for 3 years, had 4 children. She had arterial hypertension, history of appendectomy and extrauterine pregnancy localized in right ovary. In the 3rd week of Peg IFN alpha treatment abdominal pain, vomiting and fever appeared. Within 4 days the patient visited the general practitioner 3 times due to her complaints but they were attributed to common side effects of IFN. In admission the patient was in bad clinical condition; hypotension, high fever and signs of peritonitis were found. Leukocytosis (22.26×10^3/μL) with neutrophilia (16.02×10^3/μL), decreased hemoglobin level (10.4 g/dL), metabolic acidosis, raised creatinine (4.1 mg/dL) and urea (121 mg/dL) levels were found in blood tests. Abdominal ultrasound revealed aperistalsis and enlarged liver with poor intrahepatic vascular presentation and plain abdominal X-ray exam showed subileus signs. On the admission day, emergency laparotomy was performed which revealed left tubo-ovarian abscess; left adnexectomy with peritoneal lavage and drainage was done. In microbiology tests *Streptococcus intermedius* susceptible on penicillin (anaerobial culture) was identified in purulent discharge from peritoneal cavity. After surgery and subsequent antibiotic treatment with amoxicillin/clavulanate and metronidazole general clinical status improved within 2 days. Treatment with interferon alpha and ribavirin has been interrupted and suspended for three months.

DISCUSSION

Serious infections are rare complications during IFN-therapy. They have been described in 0.7% (30/4234) in WIN-R study during therapy with Peg IFN alpha 2b plus RBV and 0.34% (2/572) in the largest Polish study of therapy with Peg IFN alpha 2a plus RBV (Jacobson *et al.* 2007; Juszczyk *et al.* 2005). Our clinical experience is consistent with above mentioned studies. In our centre between October 2004 and June 2008, 543 patients with chronic hepatitis HCV were treated with pegylated interferon alpha 2a and ribavirin. Therapy was prematurely discontinued due to adverse events in 56 cases, including 5 cases because of severe bacterial infection (0.92%).

In this paper we report two cases of serious gynecological infection (TOA) in women after 40th year of age, without any significant preexisting risk factors of this type of infection.

PID and TOA typically affect young, childless, sexually active women with multiple partners, not using condoms, with intrauterine devices as a birth control or with previous episodes of PID. Changes in the vaginal flora, composition of the mucus plug, and cervical cell type are believed to affect the risk of infection. TOA most commonly occurs as a result of bacterial infection of the cervix or vagina, then ascending into the endometrium, fallopian tubes, ovaries, and adjacent structures. Less commonly, direct spread from a nearby infection such as appendicitis or diverticulitis may occur. Hematogenous infection is rare (Chia & Huang 2006; Halperin *et al.* 2003). There are some recognized factors predisposing to serious infections during IFN treatment. The most important ones are liver cirrhosis and severe neutropenia (<500 cells/ul), although the latter is still under debate (Antonini *et al.* 2008).

In our patients traditional risk factors of either PID or IFN-associated infections did not appear. They were older than the most predisposed age group (20–40 year of age); had one regular sexual partner; were also HIV-negative. Before IFN therapy patients were under gynecologic care, without apparent signs or symptoms of PID and without concomitant or previous pelvic pathology. They both were multiparae. None of patients was cirrhotic or neutropenic at the time of developing infection. Both infections developed in different time of therapy, in the first case long time after transient period of neutropenia and in the second case at the beginning of treatment (3 weeks), without apparent neutropenia.

The strains of the genus isolated from the both of patients constitute the human normal flora. The viridans streptococci are dominant groups of the resident flora of the oral cavity and pharynx in all age groups. *Streptococcus intermedius* (anginosus group) is regular member of the commensal bacteria on tooth surfaces of man, in particular in the gingival crevices. The strains of this genus are noteworthy for their participation in opportunistic infections, including brain, splenic and liver abscesses (Matsubayashi 2007). *Porphyromonas asaccharolytica* belong to the non-sporing anaerobes, which are found in the mouth, gastrointestinal tract and female genital tract of healthy individuals as part of the commensal flora. They may occur in abscesses and soft tissue infections in various localizations. *P. asaccharolytica* strains are rarely isolated in pure culture – they are often found in association with facultatively anaerobic or aerobic organisms (Jover-Díaz *et al.* 2003). We conclude that pegylated interferon therapy may reveal severe pelvic inflammatory disease caused by organisms of human normal flora. Disease severity followed by opportunistic infections did not correspond with pathogenicity of isolated strains but hosts' condition. In both presented cases the risk factor could be immunomodulatory effect of pegylated interferon therapy. No association of infection with neutropenia was observed. We cannot exclude previous asymptomatic or subclinical infections in our patients, which could progress silently to the TOA stage and was not noticed on routine gynecologic exam.

Serious infection in described two cases had significant influence on treatment of hepatitis C outcome; in first case caused interruption in therapy for 3 weeks and was probable important factor of therapy failure. In the second one IFN therapy had to be suspended and has not been reintroduced within subsequent three months. Moreover, both infections were life-threatening, one of them progressed to septic shock with acute renal failure. Both patients required surgical treatment.

We do not state a direct link between IFN therapy and above described infections but it appears possible. In our patients infections developed during IFN treatment; typical risk factors of TOA were absent; the causative pathogens were opportunistic bacteria. As these episodes were life-threatening and significantly influenced treatment course we suggest that even in older women, without apparent risk factors of PID careful gynecological exam is needed as routine element of baseline evaluation before starting and during Peg IFN therapy.

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