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案例報告

Drug fever associated with ciprofloxacin in a cirrhotic patient with hepatocellular carcinoma

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Running title: Ciprofloxacin-induced drug fever

ABSTRACT

Fever is a common problem encountered by physicians daily. Among the etiologies, drug fever is relatively difficult to be diagnosed. Un-recognition of drug fever will expand medical expenditure massively by extra testing, empiric therapy, and longer hospital stays. This case report describes a cirrhotic patient of hepatocellular carcinoma who developed a drug fever 2 days after introducing ciprofloxacin to control bacterial infection complicated with transcatheter arterial chemoembolization (TACE). The fever was associated with relative bradycardia without eosinophilia. Infections and sequelae of TACE were excluded. A Naranjo score of 6 points favored the probability of drug fever related to ciprofloxacin. Our experience could remind physicians that drug fever should be suspected in febrile patients with relative bradycardia after excluding other possibilities and ciprofloxacin could be one of the etiologies.

Key Words: Ciprofloxacin, Drug fever, Relative bradycardia.

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INTRODUCTION

Fever can be the sole manifestation of an adverse drug reaction in 3~5 % of cases [1,2]. Diagnosis of drug fever is relatively difficult because there is no laboratory test that can be applied to diagnose all cases with this disorder. Time relationship between the drug administration and the fever may be the only clue for a physician to suspect drug fever. Un-recognition of drug fever will expand medical expenditure massively by extra testing, empiric therapy, and longer hospital stays. Therefore, early diagnosis of drug fever to remove offending agents is very important in clinical practice. Drug fever is defined as a disorder characterized by fever without cutaneous manifestations coinciding with the administration of the drug and disappearing after the discontinuation of the drug, when other possibilities are excluded[3,4]. Fever is a common problem encountered by physicians daily. Among the etiologies of fever, infection is the most common reason[5]. Therefore, antimicrobials and antipyretics are commonly prescribed. However, antimicrobials and antipyretics are also the most common causes of drug fever[6]. Ciprofloxacin is one of the most commonly used antimicrobials for severe bacterial infection. Several adverse drug reactions (ADR) have been reported about pyrexia of uncertain importance in patients receiving ciprofloxacin[7,8]. However, no direct evidence supports the relationship between ciprofloxacin and drug fever. Reported ADR might, possibly be related to the drug. Therefore, further evidence is needed to support the relationship between ciprofloxacin and drug fever. To our knowledge , this might be the first case report of this association.

CASE PRESENTATION

A 66-year-old male patient had liver cirrhosis and hepatocellular carcinoma (HCC). He was admitted to receive the 5th transcatheter arterial chemoembolization (TACE) for the recurrent small HCC of 1.5 cm in size. Fever developed on the 2nd day after TACE (Figure 1). Initially, supportive management was given only. However, the patient had pneumobilia and history of post-embolization biliary tract infection that predisposed to recurrent infection. Associated tachycardia, shaking chills and spiking fever during the next 5 days made superimposition of bacterial infection highly suspected. Ciprofloxacin empiric therapy was prescribed. With an initially rapid of body temperature (Figure 1), fever rebounded 3 days after ciprofloxacin therapy. However, there was no evidence of airway or urinary tract infection, no abdominal pain, no painful skin lesion, and no headache with rigid neck. Patient felt comfortable during spiking fever with relative bradycardia, defined as the pulse rate rises less than 15 beats/min for each degree centigrade of fever[9]. The fever pattern was mildly changed by the use of acetaminophen. The serum C-reactive protein (CRP) and α-fetoprotein (AFP) levels progressively decreased from 250 to 127 μg/mL and from 165 to 65 ng/mL, respectively. Repeated blood cultures were all negative. Although the eosinophil count was normal (112 cells/μL), drug fever caused by ciprofloxacin was considered. Fever improved in the next day after withdrawal of ciprofloxacin and the body temperature returned to near normal in the 3rd day.

The Naranjo adverse drug reaction (ADR) probability scale criteria[10] were used to evaluate the relationship between ciprofloxacin and drug fever. By the fact that relative bradycardia supported the diagnosis of drug fever and alternative explanations had been excluded, the Naranjo score for ciprofloxacin in our patient was 6 points (Table 1).

DISCUSSION

Diagnosis of drug fever needs to meet three criteria[3,4]. First, fever coincides with the administration of the drug. Second, fever disappears after the discontinuation of the drug. Third, other causes for the fever are excluded after careful physical examinations and laboratory investigations. Our patient fulfilled all of the above criteria. The first, time to onset of drug fever could range from less than 24 hours to many months (median eight days)[6]. Our patient developed fever 3 days after ciprofloxacin therapy. The second, most of the drug fever usually resolves within 48 to 96 hours of discontinuing the offending drug[11]. Ciprofloxacin was discontinued and fever subsided 48 hours later. The third, other causes for the second episode of high fever, including infections and complications of TACE, were excluded. Fever developing after TACE is one of the most common complications. Therefore, the first febrile episode could be related to TACE. However, the TACE-related, post-embolic fever is usually only mild and transient[12,13] and most often occurs soon after the procedure[12,13]. Our patient developed spiking fever with chills. These characteristics were quite different from the post-embolic fever reported before[12,13] so that other etiology should be excluded. Our patient had liver cirrhosis, HCC and pneumobilia. Deficiency of bactericidal and opsonic activities, impaired phagocytic activity, and low levels of serum complements could exist in cirrhotic patients[14]. This immunocompromised state could predispose to bacterial translocation, bacteremia and occult sepsis[14]. Furthermore, there is a marked decrease of kupffer cells within HCC to defend against infection[15]. Arterial embolization during TACE could block the blood stream and interfere with immunocompetent cells getting into the tumor part to combat invading organisms. Moreover, pneumobilia might facilitate intestinal bacteria getting into the intrahepatic biliary system to cause infection. Therefore, infection was highly suspected for the first febrile episode. Empiric antibiotic therapy was given with ciprofloxacin and the fever improved quickly. High fever recurred 3 days after ciprofloxacin therapy. There were several possibilities of this recurrent fever, including uncontrolled infection or tumor necrosis caused by TACE. However, these possibilities were not supported by the progressive decrease of CRP levels. Another possibility was drug fever caused by newly administered drugs with a fever pattern ranging from single low-grade pattern to spiking fever with shaking chills[3,4]. Only ciprofloxacin and acetaminophen were prescribed after TACE. Acetaminophen was only prescribed after onset of fever. Therefore, ciprofloxacin could be the most possible agent to cause drug fever. The time-relationship between prescription of ciprofloxacin and occurrence/disappearance of fever supported the diagnosis of ciprofloxacin-induced drug fever. Re-challenge with the agent can confirm the diagnosis if fever recurs within a few hours[11]. However, re-challenge may be associated with unwanted events[6] and is not often performed. Ciprofloxacin became available 20 years ago. There was little information concerning ciprofloxacin-induced drug fever. This could be due to unreported side effect causing neglect of physicians, masking by associated disease, and/or patient specificity. Our patient had liver cirrhosis and HCC that could change the pharmacokinetics of fluoroquinolones [16] and/or their drug-drug interactions. Therefore, after exclusion of other possibility, ciprofloxacin induced drug fever was highly impressed.

Other objective evidence was the presence of relative bradycardia. When fever occurred, the pulse rate rises about 15 beats/min for each

degree centigrade of fever[9]. Relative bradycardia exists when this expectation is not found[9]. Relative bradycardia can be associated with several infectious diseases, including legionnaires' disease, psittacosis, typhoid fever, mycoplasma pneumonia, brucellosis, dengue, yellow fever, tuberculous meningitis, blackwater fever, and non-infectious diseases such as factitious fever (manipulation of thermometer for secondary gain) and drug fever[9,17]. Although drug fever-associated relative bradycardia is found only in 10% of patients[4], relative bradycardia could be a useful clue when it is present. Our patient felt coomfortable with relative bradycardia during the second febrile period (Figure 1) that gave us a useful clue. Another clue of drug fever is eosinophilia. Eosinophil count varies with age, exercise status, and environmental allergen exposure. Blood eosinophil counts also have diurnal change with lowest level in the morning and highest at night[18]. The differential diagnosis of eosinophilia includes parasitic infections, allergic diseases, and neoplasms[18]. Medications, such as glucocorticoids and adrenaline therapy, can decrease eosinophil counts[18]. Our patient did not have eosinophilia and/or misleading medications. Therefore, clinicians might make the diagnosis of drug fever less likely. However, eosinophilia occurred only in less than 20 % of patients with drug fever[4]. Therefore, normal eosinophil count cannot exclude the possibility of drug fever. There are five possible mechanisms of drug fever[1-3,19,20], including hypersensitivity reactions, altered thermoregulatory mechanisms, direct pyogenic effect related to administration of the drug, extension of the pharmacologic action of the drug, and idiosyncratic reactions. Hypersensitivity is the most common cause among these mechanisms[1,3,4,11]. Among the reasons of hypersensitivity, immunologic reaction mediated by drug-induced antibodies might be the most common one[11]. Ciprofloxacin could induce reversible arthralgia[21,22] which is commonly induced by immune complex. Therefore, there is a biological plausibility of drug fever induced by ciprofloxacin. A Naranjo score of 0 or lower indicates that ADR is unlikely to be related to the drug, a score of 1–4 indicates a possible relationship, a score of 5–8 indicates a probable relationship, and a score of 9 or above indicates that the drug definitely caused the ADR. The Naranjo score of 6 was found in our report. This supported a probable relationship between drug fever and ciprofloxacin. However, more evidence is required and the exact mechanism of drug fever caused by ciprofloxacin still needs to be clarified.

In conclusion, drug fever should be suspected in febrile patients with relative bradycardia after excluding other possibilities. Ciprofloxacin can have the possibility of inducing drug fever. Early diagnosis of ciprofloxacin induced drug fever could improve the quality of medical care.

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Table 1. Naranjo adverse drug reaction probability scale

	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse reaction reappear when the drug was re-administered?	+2	−1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	−1	+1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
			total scores:	+6

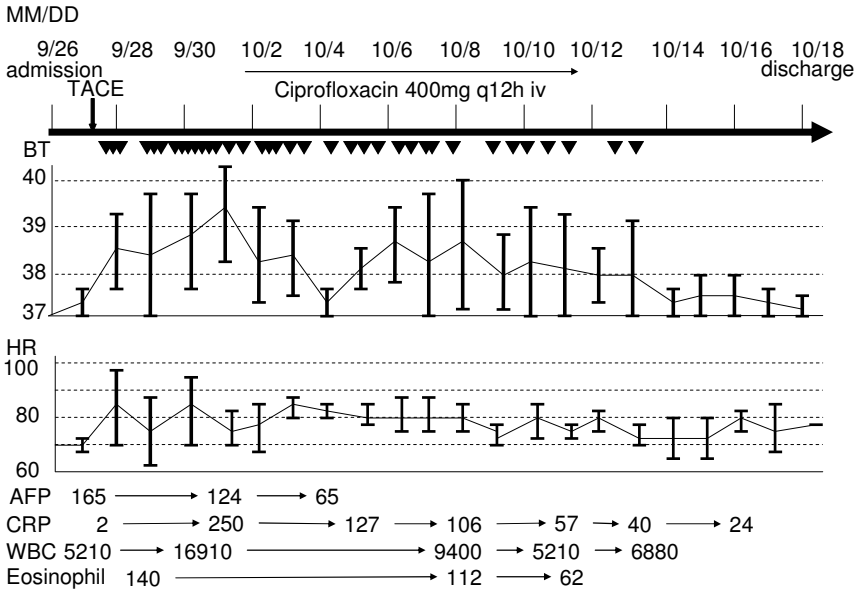

Figure 1. Clinical course of the patient. ▼: Acetaminophen therapy; AFP: α-fetoprotein (ng/mL); BT: body temperature (℃); CRP: C-reactive protein (μg/mL); Eosinophil: eosinophil count (cells); HR: heart rate (beats/minute); iv: intravenous injection; MM/DD: month/day; TACE: transcatheter arterial chemoembolization; WBC: white blood count (cells/μL).

Ciprofloxacin引起藥物熱：案例報告和文獻回顧

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本案例報告目的是描述 ciprofloxacin 引起的藥物熱。由於幾乎每一種藥物都可能會引起藥物熱，因此診斷藥物熱相當困難，而未診斷的藥物熱，會產生多餘的檢查、治療及增加住院天數，從而造成健保總額預算下醫院的財務負擔，因此早期正確的診斷藥物熱，可以增進醫療品質並改善醫院財務負擔。案例病人是住院接受經導管肝動脈化學栓塞(transcatheter arterial chemoembolization;TACE) 處理 1.5 公分肝癌的患者。病人在 TACE 後第二天開始發燒合併寒顫持續 5 天，因伴存高 CRP 和白血球增多，懷疑感染症而給予 ciprofloxacin 治療。治療開始後病情有顯著進步且發燒已改善,但隨後再出現尖峰性發燒(spiking fever) 合併相對性心搏過慢 (relative bradycardia)，病人臨床表現仍相當輕鬆，經過詳細的理學及實驗室檢查，沒有發現其他發燒病因，也未出現嗜伊紅性白血球增多症(eosinophilia)，在高度懷疑 ciprofloxacin 引起的藥物熱而停藥後，發燒於次日漸漸自行消退。以 Naranjo 藥物不良反應評分表評估為 6 分，顯示 ciprofloxacin 很可能 (probable) 可以引起藥物熱。由於 ciprofloxacin 未曾被報導會引起藥物熱。我們的經驗可提供臨床醫師往後處理疑似 ciprofloxacin 引起藥物熱之參考。

關鍵字：ciprofloxacin，藥物熱，嗜伊紅性白血球增多症，相對性心搏過慢。