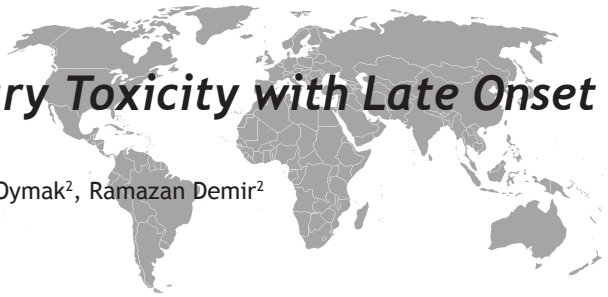
# *Gemcitabine Induced Pulmonary Toxicity with Late Onset*



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***ABSTRACT***

*Gemcitabine is a nucleoside analog that has been increasingly used in the chemotherapy of solide tumors, including breast, pancreas ovary and non small cell lung cancer. It is generally well tolerated and has few side effects. Gemcitabine induced pulmonary complications range from mild dyspnea to death from ARDS. A 57- year- old man was treated with six cycles of gemcitabine because of pancreatic carcinoma in July, 2004.The patient had self limiting weakness, lack of appetite, nausea and no dyspnea in treatment period. One year later, he was admitted to a local hospital with exercises induced dyspnea. He had been given levofloxacin for 14 days. On admission to our hospital, his complaint kept on. A few inspiratory crackles were present at right base. CXR demonstrated interstitial infiltrations in the right lung lower zone. HRCT showed grand glass opacity and mild reticular patterns in right lung middle and lower lobes. Bronchoscopy was performed. Transbronchial biopsy revealed nonspecific interstitial pneumonia. Following the administration of oral corticosteroid, he had complete resolution of all signs and symptoms of gemcitabine toxicity.*

***Key words:*** *Gemcitabine, nonspecific interstitial pneumonia, drug toxicity*

## *Geç Başlangıçlı Gemsitabine Bağlı Akciğer Toksisitesi*

***ÖZET***

*Gemsitabin küçük hücreli dışı akciğer , pankreas , mesane , over ve meme kanseri gibi solid tümörlerde kullanımını gittikçe artan bir nükleozid analoğudur.Genelde iyi tolere edilir ve nadiren yan etkiler görülür.Gemsitabine bağlı pulmoner komplikasyonlar hafif dispneden ARDS sonucu ölüme kadar değişebilmektedir. 57 yaşında erkek hasta pankreas kanserine bağlı 6 siklus gemsitabin monoterapisi almış. Tedavi sırasında nefes darlığı olmaksızın halsizlik, iştahsızlık ve bulantı şikayetleri olmuş. Bir yıl sonra eforla gelen nefes darlığı nedeniyle dış merkeze başvurmuş ve 14 gün levofloksasin tedavisi almış. Bizim hastanemize başvurduğunda şikayetleri devam etmekte idi. Fizik muayenesinde sağ bazalde ralleri vardı.Çekilen Akciğer Grafisinde sağ akciğer alt zonda interstisyel infiltrasyonlar görüldü. HRCT de sağ akciğer orta ve alt loblarda buzlu cam manzarası ve ılımlı retiküler patern görüldü. Yapılan bronkoskopi sonucu alınan transbronşial biopside nonspesifik interstisyel pnömoni saptanıldı.Oral kortikosteroid tedavisini takiben gemsitabin toksitesinin bütün bulgu ve semptomlarının gerilediği görüldü.*

***Anahtar kelimeler:*** *Gemsitabin, nonspesifik interstisyel pnömoni, ilaç toksisitesi*

## INTRODUCTION

Gemcitabine (2',2'-difluoro-2'deoxixitidine) is a chemotherapatic agent and an antimetabolite (1). Alone or inside the combinations, it is used for non small cell lung cancer, pancreas, bladder, over and breast cancer. It has been used since 1989. Generally it has simple side effects. These are; flu-like symptoms, nausea, vomitting and also bone marrow depression may be seen depending on the dosage (1-4). First pulmonary toxicity is mentioned in 1997 (5). In this system the most common side effect is mild and temporary dyspnea (1,4,6,7). It is recorded in 8-10% of the cases (6,7). Acute respiratory distress syndrome (ARDS) is also reported. Some of these cases may be fatal (5). Long term side effects are reported as interstitial covers (4). This time period is 3-4 months (3,4). As the clinical usage of gemcitabine increased, the side effects become more important. In our case report, gemcitabine was given to a patient with pancreas cancer and

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the side effects occured after a year were reported like dyspnea, interstitial infiltration and nonspecific pneumonia which were seen with biopsy. As it was the latest pulmonary toxicity in the literature, it was discussed with the rest of gemcitabine induced pulmonary toxicities.

## CASE

A 52- year- old male patient with pancreatic carcinoma was surgically operated. He was reported as inoperable because of the multiple lymph nodes seen in the abdomen during operation. In July 2004 he took 6 cycles of gemcitabine monoterapy once in 15 days. During this therapy dyspnea wasn't reported in the patient having self limiting weakness, lack of appetite and nausea. In October 2005 he had visited a health center because of dyspnea and took levofloxacin for 14 days. On admission to our hospital, his complaints kept on. His body temperature was normal but cracles were detected in the right basal during the physical examination. White blood cell was 6950 mm3 and sedimentation rate was 45 mm/hour. There wasn't any coroner arterial disease or cardiac insufficiency. According to the echocardiography, left ventricle functions were normal and ejection fraction was reported as 79%. In the chest X-ray there were interstitial infiltrations at the right inferior zone and high resolution computed tomography (HRCT) (Figure 1) showed that appearance of ground glass opacities in the right middle lobe lateral segment and right pulmonary inferior lobe basal segment and also moderate reticular appearances were detected in the peripheries. There was not any pathology in the bronchoscope but nonspecific intersititial pneumonia was detected in the transbronchial pulmonary biopsy (Figure 2). Blood gas analyses were: pH:7,43 $PaO_2$:56.5 $PaCO_2$:32.1 and $satO_2$:84.3%. DLCO 74% and DTPA clerens showed fast alveolar epithelial permeability in both of the lungs. ANA and anti ds DNA were negative. 60 mg fluocortolone therapy was started. At the end of the first week of the treatment, respiratory complaints disappeared and at the end of the first month the radiological and spirometric findings were normal.

## DISCUSSION

Gemcitabine is a relatively new nucleoside analog and used in solid organ tumors (1,2,5). There are several pulmonary toxicities that are reported. The most common side effect seen in 8-10% of the cases is temporary dyspnea (1,4,6,7). Our patient didn't complain about dyspnea. This temporary dyspnea is usually seen with bronchospasm (3). As it disappears, treatment is not necessary for this symptom. On the other hand gemcitabine induced serious dyspnea was reported in 3-5% of the cases (5,8,9). In these cases giving up the drug, diuretics and corticosteroids were generally enough. But sometimes acute lung injury occurs (4,5,9,10). Some of them got better with high doses of corticosteroids but some of the patients died in short term (3,5,9). In autopsy studies, similar to other nucleoside analogs that acute lung damage shows a structural resemblance it is shown that with capillary leaks there were concentrated intraalveolar protein and noncardiogenic pulmonary edema with interstitial inflammation (3,7). In our case there weren't any complaints about dyspnea and other respiratory problems.

Gemcitabine induced pulmonary toxicities may be seen in short or long terms with a latent period. In the literature it is mentioned that this period may be 4 months (4). The symptoms in our case started a year after the beginning of treatment. There aren't any cases in the literature which have such long term symptoms.

Diagnose of drug induced pulmonary diseases is not easy. Especially in long term symptoms other diagnoses have to be excluded. First of all, tumor expansion, congestive heart diseases, infectious diseases and autoimmune diseases have to be excluded. In our case levofloxacin treatment was first given with the thought of infections. Echocardiography showed that the ejection fraction was 79%; for this reason we have excluded heart diseases. ANA and anti ds DNA tests were made. The results were normal. The culture of bronchial lavage fluid was negative and transbronchial biopsy was showed nonspecific interstitial lung disease. The complaints of the patient including interstitial infiltration in the right pulmonary inferior zone, decrease in DLCO, increase in the DTPA, made us to think interstitial pulmonary disease. The patient had a history of gemcitabine use, so these symptoms are attributed to gemcitabine toxicity. Boisella et al (11) found out ground glass opacities, septal thickness and reticular infiltration in three cases with CT. They also mentioned that these infiltrations may be both symmetric and asymmetric. As our HRCT findings are similar to the findings mentioned by Boisella et al, we thought about gemcitabine induced pulmonary toxicity with late onset.

When we evaluated our case from the prespective of tumor expansion we saw that Ca19-9, abdominal ultrasound (USG) and CT were normal. We didn't focus on the lymphangitic expansion because we haven't detected any septal thickness and nodules in HRCT. We used bronchoscope to guarantee the results and we found out nonspecific interstitial pneumonia. The culture of bronchial lavage fluid was negative and transbronchial biopsy

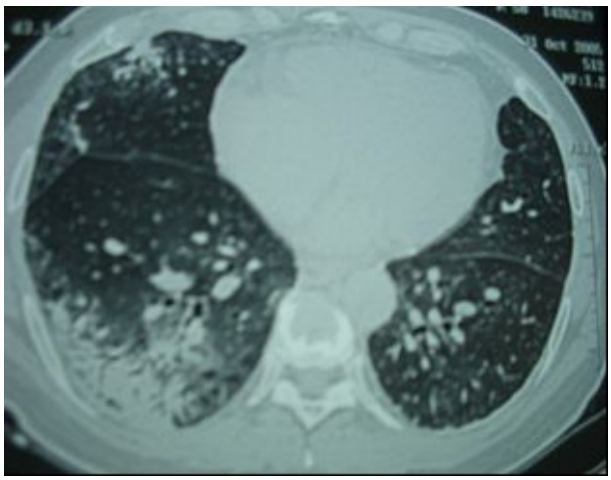

***Figure 1**. Ground glass opacities at right lung and moderate reticuler appearances at peripherals with HRCT*

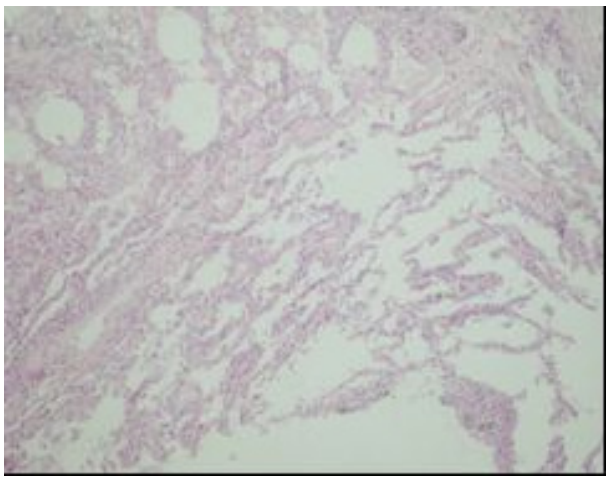

***Figure 2**. Thickness in alveolar membrane and lymphocyte infiltration are seen in figure. (HE,X100)*

showed nonspecific interstitial pneumonia. According to the literature if ARDS is seen in acute period, mainly capillary leaks, diffuse alveolar deficiency and disseminated intravascular coagulation are detected (3,5). In long term cases especially nonspecific interstitial pneumonia is detected. In our case, structure of the alveoli were normal, alveolar lumen was open but interstitial interval was thick and there were mononuclear cell infiltrations with lymphocytes (Figure 2). As a result we thought that it was the result of nonspecific interstitial pneumonia.

60 mg fluocortolone treatment is given to the patient. At the end of the first week of the treatment, respiratory complaints disappeared and at the end of the first month the radiological and spirometric findings were normal. We are still following the patient and he hasn't got any respiratory symptoms.

Our case is the first in the literature as gemcitabine induced pulmonary toxicity with late onset. In cases with controlled primary tumors, long term interstitial pulmonary disease may depend on gemcitabine usage and we showed this with our case.

Gemcitabine is a popular anti-metabolite and its usage will continue increasingly. In all of the cases with complaints of dyspnea, cough and intersititial infiltrations after the gemcitabine treatment we have to think about gemcitabine induced pulmonary toxicity with late onset. As a result we were able to treat this side effect with corticosteroids.

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