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# Contents

<b>1-Re-Irradiation in the Treatment of Pediatric Central Nervous System Tumor Recurrence ....</b>	<b>1 - 6</b>
A Single-Center Results	
<b>2-Is restless legs syndrome associated with Helicobacter pylori infection?.....</b>	<b>7 – 14</b>
<b>3-Autoimmune Diseases in Patients Hospitalized with COVID-19.....</b>	<b>15 – 25</b>
<b>4-Coexistence of Brucellosis and Mushrooms Intoxication in a Patient Presenting with.....</b>	<b>26 – 31</b>
Toxic Hepatitis	
<b>5-Coexistence of Brucellosis and Mushrooms Intoxication in a Patient Presenting with .....</b>	<b>32-35</b>
Toxic Hepatitis	

## Re-Irradiation in the Treatment of Pediatric Central Nervous System Tumor Recurrence

Feyza Yaşar Daşgın<sup>1</sup>, Gonca Altınışık İnan<sup>1</sup>, İpek Pınar Aral<sup>2</sup>, Süheyla Aytac Arslan<sup>2</sup>, Yılmaz Tezcan<sup>2</sup>

<sup>1</sup>Ankara City Hospital, Radiation Oncology Clinic, Ankara/Turkey

<sup>2</sup>Ankara Yıldırım Beyazıt University, Radiation Oncology Clinic, Ankara/Turkey

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### ABSTRACT

**Aim:** Radiotherapy is one of the main treatment modalities in childhood cancers, but it is a treatment method that is generally cautious due to its side effects. Central nervous system re-irradiation is the treatment choice that should be applied by considering the benefit-harm balance due to its side effects, especially radionecrosis. In this study, we aimed to report the results of the cases who underwent childhood CNS reirradiation, which is very disadvantageous in terms of toxicity.

**Material and Methods:** In this study, the data of patients with primary central nervous system neoplasm who received the repeat courses of RT in our department were retrospectively analyzed. Second-course RT is called reirradiation and is defined as prescribing radiotherapy to the field which overlaps with the first radiotherapy area. Data were obtained from patient files and planning system. **Results:** Six patients were included in this study. The primary diagnosis of 50% (n=3) of the patients is medulloblastoma. In the first treatment, craniospinal RT was applied to three patients. The median time between diagnosis and recurrence was 19.5 (range 11-101) months. The median time between primary and secondary RT was 22 (range 7-102) months. The BED3 equivalent of the dose received by the brain stem (BS) due to the first radiotherapy is a median 90 (range 80.6-99.2) Gy. The primary RT BS EQD2 dose was median 52.2 (range 50-57) Gy. The median total dose of re-RT is 36 (range 20-50.4) Gy. The median BED3-BS for re-RT is 48.4 (range 11.5 -90) Gy. The median EQD2 brainstem for re-RT is 29 (range 7.2-54) Gy. During the follow-up period, 3 patients died. Three patients are alive at their 7, 12, and 27-month follow-ups and have no health problems related to the primary diagnosis.

**Conclusion:** Radio necrosis was not detected in any of the living cases in our study. Further studies are needed to select the appropriate patient and radiotherapy technique for reirradiation in pediatric CNS cases

## ***Introduction***

CNS (Central nervous system) tumors constitute 20% of childhood tumors and are responsible for 30% of cancer-related deaths<sup>1</sup>. Frequently observed CNS tumors are, medulloblastoma, low and high-grade gliomas, and ependymomas. Combined modality therapy with chemotherapy, surgery, and radiotherapy is the standard treatment approach. However, recurrence can be observed in 30% of the patients usually with a dismal prognosis, and salvage treatment may be required. Management of these relapses is often challenging since there is little evidence to guide the decision-making process. Retrospective series have demonstrated long-term disease control e.g in ependymoma and medulloblastoma with second-course radiotherapy suggesting that Radiotherapy (RT) is a critical component of the multidisciplinary approach both in de-novo and recurrent tumor management. However, the developing pediatric brain is sensitive to radiation, and reirradiation (re-RT) must be weighed carefully against the acute and late effects<sup>2,3</sup>.

In recent years, an increasing number of papers published regarding experience on re-RT of recurrent childhood tumors<sup>4-9</sup>. They are usually small case series and heterogeneous in almost all aspects including tumor type, surgical technique, chemotherapy regimen, and radiotherapy dose and fractionation. Since there is no possibility of a randomized trial with high-level evidence in the short term, so for now at least decisions must be guided on retrospectively reported clinical experience which makes this case reports valuable. Hence, we aimed to report the results of reirradiation for CNS recurrence applied to 6 pediatric patients treated at the Radiation Oncology Clinic of Ankara City Hospital within 2 years.

## ***Materials and Methods***

In this study, the data of patients with primary central nervous system neoplasm who received the repeat courses of RT in our department were retrospectively analyzed. Second-course RT is called reirradiation and is defined as prescribing radiotherapy to the field which overlaps with the first radiotherapy area. Patient examination information, patient files, RT plan details, and electronic system data were used for the study. Data regarding gender, primary histological type, age at the time of diagnosis and recurrence, the time between diagnosis and recurrence, age at the time of first-course RT and reirradiation, the time between two RT courses, location of primary disease, and recurrence data were obtained from patient files and planning system. The aim of the study was the time between primary and secondary RT and patients' compliance with treatment. Additionally, the localization and interval between RT were noted for a patient undergoing a different site RT.

### ***Patients Selection***

Pediatric patients who underwent re-RT for cranial spinal tumors in Ankara City Hospital between 14.03.2019 and 01.04.2022 were included in the study. Patients with missing data, out of follow-up, and patients over the age of 18 were excluded from the study.

### ***Compliance with ethical standards***

This study was carried out by the principles of the Declaration of Helsinki, considering these principles. Ethics committee approval was obtained for this study from Ankara Provincial Health Directorate, Ankara City Hospital, Clinical Research Ethics Committee No. 1 with the ethics committee number E1-21-1504 on 03/02/2021.

### ***Results***

Six patients who underwent CNS re-RT in Ankara City Hospital between 14.03.2019 and 01.04.2022 were evaluated retrospectively. The patients received multimodal treatment with surgery, chemotherapy, and radiotherapy according to their age and tumors first-line therapy. Patients who developed recurrences during their follow-up underwent resection if they were operable. Patients and treatment details are summarized in Table 1.

The primary diagnosis of 50 % (n=3) of the patients is medulloblastoma. In the first treatment, craniospinal RT was applied to three patients. Primary RT was administered to patients at a fraction dose of 1.8 or 2 Gy, with a median total of 54 (range 23.4-60) Gy. The BED3 equivalent of the dose received by the brain stem due to the first radiotherapy is a median 90 (range 80.6-99.2) Gy. The primary RT brainstem maximum EQD2 dose was calculated as a median 52.2 (range 50-57) Gy.

The median time between diagnosis and recurrence was 19.5 (range 11-101) months. The treatment of patients after recurrence is as follows; 3 patients (50%) CRT ; 2 patients (33.3%) surgery and RT; 1 patient (16.7%) Surgery + CRT. Local field Re-RT was applied to 3 different relapse sites of the patient who was diagnosed with high-grade glial tumors. Re-irradiations were planned using the IMRT and SRT techniques. The median time between primary and secondary RT was 22 (range 7-102) months. The median total dose of re-RT is 36 (range 20-50.4)Gy. The median BED3 for re-RT Brainstem is 48.4 (range 11.5 -90) Gy. The median EQD2 for the report brainstem is 29 (range 7.2-54) Gy.

During the follow-up period, 3 patients died. The causes of death of the patients were pneumonia, sepsis, and GIS bleeding. The remaining patients with two anaplastic ependymomas and one MB are alive. Three patients are alive at their 7, 1,2, and 27-month follow-ups and have no health problems related to the primary diagnosis.

Stable disease was reported in the follow-up imaging studies of these patients. Radionecrosis was not detected radiologically or clinically in any of the surviving patients. The third course of re-irradiation of the patient with a diagnosis of medulloblastoma under the age of 3 was interrupted at the request of the patient's family, and the patient died two months later. The technical characteristics of reirradiation are summarized in Table 2.

### ***Discussion***

In our study, the data of 6 patients who underwent cranial re-RT in our clinic were analyzed retrospectively. The median time between diagnosis and recurrence was 19.5 (range 11-101) months. The median time between primary and secondary RT was 22 (range 7-102) months. The patients were well tolerated and no serious treatment-related toxicity was observed. Radionecrosis was not detected radiologically or clinically in any of the surviving patients.

Wetmore and colleagues retrospectively reviewed 38 recurrent medulloblastoma patients of whom 14 of them received salvage RT and reported that the use of ReRT resulted in a statistically significant improvement in survival both for standard and high-risk patients compared to non-irradiated ones<sup>7</sup>. method, thereby obtaining information about the molecular subgroups of relapsed patients. They reported that patients who progressed > 4 months after the first course of RT and with focal brain recurrence experience longer survival. They also reported long-term survival for one patient with a wnt-activated subgroup and poor survival for one group 3 and 3 shh-activated subgroups after ReRT emphasizing the importance of molecular analysis in some aspects of salvage therapy decision. Emphasizing that molecular analysis may guide salvage therapy decisions. In the study of Gültekin et al., in which they evaluated hypofractionated stereotactic radiotherapy (HFSRT) treatment in children, the results of 18 cases with primary CNS tumors were reported (8). Although a separate analysis was not performed in the primary brain tumors group, it was reported that the cumulative BED value, the time between two treatments, and the treatment technique did not affect local control. They observed 2 (9%) brain necrosis (grade 3 and grade 1) at 1 and 5 months post-ReRT and concluded HFSRT was safe.

In a multicenter study, Rao et al. presented the most extensive case series of 67 patients with recurrent CNS tumors<sup>6</sup>. Among these cases, one patient experienced seizures, somnolence, and edema post-ReRT (25 Gy total in 5 fractions) interpreted as radionecrosis, managed with high dose steroids but 2 months after treatment the patient also developed tumor progression, making the initial diagnosis suspicious.

We observed neither clinical nor radiological radionecrosis after conventionally fractionated ReRT with IMRT, although it is difficult to draw definitive conclusions with the short follow-up period and the small number of cases.

In all these studies, there is no optimal recommended RT technique or dose. As mentioned before, with the advances in radiotherapy, an increasing number of pediatric patients are treated with reirradiation salvage therapy. However, it is impossible to reach precise results due to the differences in radiotherapy dose, technique, recurrence pattern, presence of accompanying surgery, and systemic agents in current studies<sup>10,11</sup>.

Proton therapy is another promising radiotherapy method in ReRT applications<sup>12</sup>. In the study reported by Farnia et al, re-irradiation results were reported in patients whose first treatment was also administered with proton therapy. No patient developed central nervous system necrosis requiring treatment. Although our center is new, 6 cases in 2 years show that these cases are increasing. Treatment decisions for these patients must be made in multidisciplinary meetings, and survival expectancy and toxicity possibilities must be considered. With improving techniques, radiotherapy has become increasingly involved in the treatment of CNS relapses, and the initial results are promising.

### ***Limitations of the Study***

The retrospective design of this study, the small number of cases, and the limited follow-up period do not make it possible to reach a general conclusion about the subject studied. However, since the subject has been reported with a limited number of cases in the literature, it was thought that this report would contribute to the literature.

### ***Conclusion:***

Following the rapid development of radiotherapy techniques, reirradiation therapies, which were not considered to be applied before, are increasingly used in childhood CNS relapses. More studies are needed for appropriate patient and treatment selection.

### ***Conflicts of interest***

The authors have no conflicts of interest to declare.

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**Table 1.** Patient Characteristic

**Table 2.** Characteristics of patients' first radiotherapy and re-irradiation plans



## Is restless legs syndrome associated with Helicobacter pylori infection?

Mustafa Kaplan <sup>1</sup>, Aysu Yetiş <sup>2</sup>, Ömer Öztürk <sup>3</sup>, Volkan Gökbulut <sup>3</sup>, Orhan Coşkun <sup>3</sup>

<sup>1</sup> Kayseri Memorial Hospital, Gastroenterology Clinic, Kayseri

<sup>2</sup> Ahi Evran University Training and Research Hospital, Neurology Clinic, Kırşehir

<sup>3</sup> Ankara City Hospital, Gastroenterology Clinic, Ankara

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### ABSTRACT

**Objective:** In this study, we aimed to investigate the frequency of restless legs syndrome (RLS) in patients with and without helicobacter pylori (HP) detected in pathology.

**Material and Method:** This study was carried out prospectively between January-June 2019 with patients who had dyspeptic complaints and underwent upper gastrointestinal endoscopy and biopsy. The frequency of RLS was compared between the two groups by applying a questionnaire to patients with and without HP.

**Results:** The study was carried out with 96 patients, 72 HP positive and 24 HP negative. Fifty-two of the patients were women (54%) and 44 were men (46%). The mean age of patients was 44. When the positivity of patients in terms of HP was examined, 1+ HP in 24 patients (25%), 2+ HP in 24 patients (25%) and 3+ HP in 24 patients (25%) were detected. Thirteen patients were diagnosed as RLS with the questionnaires (14%). The average age of these patients was 41. Nine patients were women (69%) and 4 patients were men (31%). Only two of these patients smoked (15%). When patients were classified according to whether they had HP or not, the rate of RLS was 8.3% in patients who were HP negative, while this rate was 12.5% in patients with 1+ HP, 12.5% in patients with 2+ HP and 21% in patients with 3+ HP.

**Conclusion:** In this study, it was shown that the rate of RLS was 14% in patients with dyspeptic complaints who had endoscopy and the rate of RLS increased with HP severity.

## ***Introduction***

Restless legs syndrome (RLS) is a disease that causes unpleasant or uncomfortable sensations in the legs and an irresistible urge to move them <sup>1</sup>. The onset and/or increase of symptoms at rest and relief with movement are typical and diagnostic for the disease <sup>2</sup>. RLS is one of the most common diseases of the nervous system and its prevalence varies between 2% and 10% <sup>3</sup>. It is more common in women and the elderly <sup>4</sup>. RLS has a familial predisposition, but the etiology of the disease is not fully known. Although most of them are idiopathic, secondary forms associated with iron deficiency anemia, chronic kidney failure, pregnancy and rheumatic diseases can also be seen <sup>5</sup>. RLS has been shown to be associated with many gastrointestinal diseases <sup>6-8</sup>. Bacterial overgrowth, infections such as HIV, Hepatitis C, and other gastrointestinal inflammatory or infectious diseases are blamed in the etiology of RLS <sup>9-11</sup>.

*Helicobacter pylori* (HP) is a microorganism primarily associated with the gastrointestinal tract, but it has also numerous extra-intestinal manifestations. Although it was previously associated with many neurological diseases such as Alzheimer's, multiple sclerosis and Parkinson's <sup>12-14</sup>, there is only one study investigating the relationship between HP and RLS <sup>15</sup>. In this study, the use of serological tests instead of the pathological Sydney classification for HP positivity and the low number of patients constitute important disadvantages for the study <sup>16</sup>. Therefore, the relationship between HP and RLS still remains unclear.

In this study, we aimed to investigate the frequency of RLS before HP eradication treatment in patients with and without HP detected in pathology.

## ***Material and Method***

This study was carried out prospectively between January-June 2019 with patients who had dyspeptic complaints and underwent upper gastrointestinal endoscopy and biopsy. The frequency of RLS was compared between the two groups by applying a questionnaire to patients with and without HP. Seventy-two HP positive and 24 HP negative patients were included in the study. While patients with HP were included in the study group, patients without HP were included in the control group. Sydney classification is

used for HP entity. The frequencies of RLS were compared between the control and study groups. Patients with neurological or chronic systemic diseases (rheumatological diseases, iron deficiency anemia, diabetes, hypertension, heart failure, pulmonary disease, celiac disease, kidney disease, liver disease and inflammatory bowel disease), sleep disorders, pregnant women and patients with malignancy were excluded from the study. Also those who received any treatment for HP before the study; those who had taken a proton pump inhibitor, bismuth or antibiotics in the last 4 weeks were excluded from the study.

A face-to-face questionnaire of 6 questions was conducted with the patients, investigating the presence of RLS. In addition, the patient's smoking status, age, gender, and co-morbid conditions were recorded with this questionnaire. Those who answered positively to all 6 criteria were accepted as RLS.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Among the numerical variables, those with normal distribution are shown as mean  $\pm$  standard deviation, and those with normal distribution are shown as median (min-max). Categorical variables are expressed as numbers and percentages.

Written informed consent was obtained from all patients for the study. The study was conducted according to the ethical standards specified in the 1964 Declaration of Helsinki. Research and publication ethics were followed in our study. Ethical approval of the study was obtained from the ethics committee of XXXX University Training and Research Hospital, dated 30.10.2018 and numbered 2018-19/167.

### ***Results***

Demographic characteristics and data of the study are given in Table I. The study was carried out with 96 patients, 72 HP positive and 24 HP negative. Fifty-two of the patients were women (54%) and 44 were men (46%). The mean age of patients was 44. It was

observed that 30 patients were smokers (31%). When the positivity of patients in terms of HP was examined, 1+ HP in 24 patients (25%), 2+ HP in 24 patients (25%) and 3 + HP in 24 patients (25%) were detected. Thirteen patients were diagnosed as RLS with the questionnaires (14%). The average age of these patients was 41. Nine patients were women (69%) and 4 patients were men (31%). Only two of these patients smoked (15%). When the data of 83 patients who were not diagnosed with RLS were examined, the mean age of the patients was 45. In these group, 43 patients (52%) were female and 40 patients (48%) were male. Twenty-eight of these patients were smokers (34%).

When patients were classified according to whether they had HP or not, the rate of RLS was 8.3% in patients who were HP negative, while this rate was 12.5% in patients with 1+ HP, 12.5% in patients with 2+ HP and 21% in patients with 3+ HP.

### ***Discussion***

In this study, we investigated the relationship between RLS and HP using a questionnaire method. As a result, the rate of RLS was found to be 14% in patients with dyspeptic complaints who underwent endoscopy. In addition, it was shown that the rate of RLS increased in correlation with the presence and severity of HP.

As it is known, HP is a microorganism that is associated with almost all kinds of diseases in modern medicine, but is considered an important predisposing factor especially for the development of gastric cancer and peptic ulcer <sup>17</sup>. In recent years, many studies have shown that HP plays a potential role in the pathogenic mechanisms of different extra-gastric diseases. The role of HP in idiopathic thrombocytopenic purpura, idiopathic iron deficiency anemia, and vitamin B12 deficiency has been previously established. There is also a growing body of evidence for the association of cardiovascular, metabolic, and neurological disorders with HP. One of the studies showing the relationship of HP with other diseases is our study.

The relationship between HP and RLS is one of the newly researched topics in the literature, about which there are only two articles. Although there is a study by Rezvani et al. in the literature, there are many methodological errors in this study. Although serology positivity was high in the country

where the study was conducted, the use of antibody determination by serology, which is not a reliable method for the diagnosis of HP, is one of the most important shortcomings of the study <sup>15</sup>. The fact that the HP rate is around 20-30% in the study and control group also supports our claim. In another study conducted with patients with dyspeptic complaints and diagnosed with RLS who underwent endoscopy, no relationship was found between RLS and HP positivity <sup>18</sup>. We think there are two possible reasons for this situation. First, the diagnosis of RLS was made similar to ours in this study, but although 6 criteria were taken for the diagnosis of RLS in our study, 4 criteria were taken in this study. Another reason is that since rapid urease test was used for the diagnosis of HP in this study, no relationship could be found between HP and RLS. In our study, pathological examination (Sydney classification) was used instead of rapid urease test.

Our study was designed differently from the other two studies above. In these studies, HP rate was investigated in patients with RLS, on the contrary, in our study, the rate of RLS was investigated in patients with and without HP. In addition, the risk between HP severity and RLS development was better demonstrated in our study.

In our study, the rate of RLS was found to be 14% when all patients were examined. In previous studies with different patient groups, it was stated that the rate of RLS varied between 2-10% <sup>3</sup>. In a study conducted with pregnant patients, the rate of RLS in pregnant women was shown to vary between 10-34% <sup>19</sup>. In a study conducted with patients with migraine, it was reported that the prevalence of RLS was 19% in this patient group, and this rate was around 8% in the healthy control group <sup>20</sup>. In our study, it was shown that the prevalence of RLS, which was 8% in the group without HP, increased to 21% as the HP severity increased in biopsy. Detection of RLS in one of every 5 patients with HP 3+ is the most important finding of our study. It should be kept in mind that this situation may be related to the HP-RLS relationship mentioned in our study, especially in patients with persistent joint-muscle pain, restlessness in the legs and dyspepsia, and that this situation can be resolved with HP eradication therapy.

The most important limitation of our study is the small number of patients. Another important limitation is that we could not provide information about the role of HP treatment in improving RLS symptoms. We expect prospective randomized studies on this subject in the future.

In conclusion, in this study, it was shown that RLS is common in people with dyspeptic complaints and the rate of RLS increases in correlation with the severity of HP.

**Ethics Committee Approval:** This research complies with all relevant national regulations, institutional policies and the principles of the Declaration of Helsinki. It was approved by the Ethics Committee of XXX University XXX Medical Faculty (approval number: 2018/19-167).

**Informed Consent:** All participants' rights were protected and written informed consent was obtained prior to the procedures according to the Declaration of Helsinki.

**Author Contributions:**

Concept – M.K., A.Y.;

Design – M.K.,A.Y.,Ö.O.,V.G.;

Supervision – M.K.,A.Y.,V.G.,O.C.;

Sources – M.K., V.G., O.C.;

Materials – V.G.,O.C.;

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Writer – M.K.,A.Y.,V.G.;

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## Autoimmune Diseases in Patients Hospitalized with COVID-19

Oğuzhan Zengin<sup>1</sup>, Muhammed Fatih Acehan<sup>1</sup>, Burak Göre<sup>1</sup>, Sümeyye Çelik<sup>1</sup>, Hüsamettin

Durmuş<sup>1</sup>, Adem Çağlayan, Erbil Çümen<sup>1</sup>, Emra Asfuroğlu Kalkan<sup>1</sup>, İhsan ATEŞ<sup>1</sup>

<sup>1</sup> Department of Internal Medicine, Ankara City Hospital, Ankara, Turkey

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SARS-CoV-2.

### ABSTRACT

**Introduction:** The aim of this study is to determine the course of COVID 19 in patients with autoimmune diseases (AD), and to investigate the severity of disease, need for intensive care and mortality in these patients.

**Methods:** In this study, 125 patients who had COVID-19 and were diagnosed with autoimmune disease before, were evaluated retrospectively. Comorbidities, demographics, laboratory findings, rates of mortality, intensive care unit admission, administration of immunosuppressive treatments and length of hospital stay were collected.

**Results:** All patients had a positive SARS-CoV-2 PCR test. The most common autoimmune diseases were rheumatoid arthritis, Hashimoto's thyroiditis and inflammatory bowel diseases.

**Discussion And Conclusion:** Our results have shown diabetes mellitus (DM), neutrophil lymphocyte ratio and platelet count were found to be an independent risk factor for mortality in patients with AD.

## ***Introduction***

COVID-19 is a respiratory infection with symptoms. Although most patients experience the disease asymptotically, some patients develop acute respiratory distress syndrome, which leads to death<sup>1</sup>.

Autoimmune diseases are characterized by complement activation and systemic inflammation caused by autoantibodies<sup>2</sup>. Immunosuppressive drugs form the basis of treatment in these patients<sup>3</sup>. It has been considered in some studies that use of immunosuppressive drugs and the inappropriate immune response may increase susceptibility to COVID 19 and the severity of the disease<sup>4,5</sup>.

Some studies show that immunosuppression has a protective effect against COVID 19, on the contrary, other studies confirmed that baseline immunodeficiencies increase the severity of the disease<sup>6,8</sup>. There were not enough comprehensive studies on the conditions that affect the prognosis in autoimmune diseases. Our aim in this study is to evaluate the prognosis of COVID 19 in patients with autoimmune disease.

## ***Material And Method***

In this retrospective cohort study, 648 patients over 18 years of age, who were admitted to the Ankara City Hospital, Internal Medicine inpatient clinic between July 1 and December 31, 2020 due to COVID-19 were evaluated for eligibility. 125 patients who were previously diagnosed with autoimmune disease and hospitalized for covid were included. Diagnosis of COVID-19 was confirmed with a reverse transcription polymerase chain reaction (RT-PCR) test from nasopharyngeal swab. Ethical approval for the study was granted by the Ethics Committee of Ankara City Hospital (Date: 28/05/ 2020, Number: E1-20-674).

Comorbidities, demographics, laboratory findings, rates of mortality, intensive care unit admission, administration of immunosuppressive treatments and length of hospital stay were recorded. Mortality, intensive care unit (ICU) admission, length of hospital stay were set as outcome measures. All patients received standard of care (SOC) medications (favipiravir, hydroxychloroquine, low molecular weight heparin, acetylsalicylic acid or dipyridamole). Ethical approval and permission from the Ministry of Health was obtained.

Statistical analysis was made by Statistical Package for Social Sciences version 26. Normality of variables was analyzed by Shapiro-Wilk test. Continuous variables were expressed either as mean  $\pm$  standard deviation or as median and minimum-maximum values according to normality.

For comparison of continuous variables according to normality, the Mann–Whitney-U test or the Student’s t-test was utilized.. The Pearson’s  $\chi^2$  test and Fisher’s final test were used to evaluate categorical variables. Multivariate logistic regression analyses were performed to determine the factors related to mortality. The p-values  $<0.05$  were considered statistically significant.

## **Results**

125 patients were included in this study. Comparative clinical and laboratory characteristics of patients were presented in Table 1. A significant difference was observed between age, diagnosis of diabetes, Typical involvement on Computed Tomography (CT), need for intensive care and length of stay by comparing the deceased and survivor groups ( $p<0.05$ ). White blood cell, neutrophil, neutrophil lymphocyte ratio, platelet, C- reactive protein, procalcitonin, lactate dehydrogenase, fibrinogen, d-dimer, ferritin values which measured at 24th hour were significantly higher in the deceased group ( $p<0.05$ ). Lymphocyte levels were significantly higher in the survivor group ( $p<0.05$ ).

Comparative autoimmune disease characteristics in deceased and survivor groups were presented in Table 2. The most common autoimmune diseases were rheumatoid arthritis (%31.2), Hashimoto's thyroiditis (%26.4) and inflammatory bowel diseases (%8.8), respectively. The most commonly used drugs in patients treated for autoimmune disease were prednisolone (24%), hydroxychloroquine (17.6%) and methotrexate (9.6%), respectively. There was no significant difference between the two groups in terms of autoimmune diseases or the immunosuppressive drugs used in the treatment.

Univariate and multivariate regression analysis for mortality were presented in Table 3. In the performed univariate analysis, a significant relationship was found in terms of age (Odds ratio (OR) for the risk of mortality; 1.053 (1.017-1.090),  $p<0.05$ , 95% confidence interval [CI]), diabetes mellitus (OR; 4.094 (1.730-9.687),  $p<0.001$ , 95% CI), white blood cell (OR; 1.179 (1.049-1.326),  $p<0.05$ , 95% CI), neutrophil (OR; 1.328 (1.145-1.540),  $p<0.001$ , 95% CI), neutrophil lymphocyte ratio (OR; 1.097 (1.042-1.155),  $p<0.001$ , 95% CI), platelet (OR; 1.006 (1.001-1.011),  $p<0.05$ , 95% CI), crp (OR; 1.009 (1.004-1.014),  $p<0.05$ , 95% CI), fibrinogen (OR; 1.449 (1.137-1.847),  $p<0.05$ , 95% CI) and ferritin (OR; 1.001 (1.000-1.001),  $p<0.05$ , 95% CI) for the risk of developing mortality, respectively.

In the performed multivariate analysis, a significant relationship was found in terms of diabetes mellitus (OR; 7.435 (2.540-21.759),  $p < 0.001$ , 95% CI), neutrophil lymphocyte ratio (OR; 1.102 (1.045-1.163),  $p < 0.001$ , 95% CI), platelet (OR; 1.008 (1.002-1.014),  $p < 0.05$ , 95% CI) for the risk of developing mortality, respectively.

Diabetes mellitus, neutrophil lymphocyte ratio and platelet levels were found to be independent risk factors for mortality. The negative predictive value was 84.7 for diabetes (OR for the risk of mortality; 4.1 (1.7-9.7), 95% CI), 86.4 for neutrophil lymphocyte ratio (OR; 4.8 (2.0-11.5), 95% CI), and 89.1 for platelet (OR; 4.3 (1.6-11.4), 95% CI), respectively.

Predictive values of independent risk factors for mortality were presented in Table 4. The sensitivity and specificity for the risk of developing mortality were 56.7 and 75.8 for diabetes, 63.3 and 73.7 for neutrophil lymphocyte ratio and 80.0 and 51.6 for platelet, respectively. The AUC (Area Under the Curve) of DM (diabetes mellitus), NLR (neutrophil lymphocyte ratio) and platelet for mortality was presented in Figure 1.

## ***Discussion***

In this study, we report the comorbidities, laboratory findings and outcomes of 125 COVID-19 patients with autoimmune diseases. Comorbidities such as diabetes mellitus and hypertension are important risk factors for the disease severity and mortality in patients with COVID-19 (9). Our study demonstrated that patients who had diabetes mellitus were seen to have a higher risk for mortality due to COVID-19.

In this study, we retrospectively analyzed the comorbidities, effect of the treatment for AD and laboratory findings of 125 COVID-19 confirmed patients with AD. In our study no significant correlation was found between autoimmune diseases and treatment regimens in terms of mortality. We find that DM, NLR and platelet levels increase the risk of mortality in patients with AD. In most studies, similar to our study, pre-existing comorbidities were shown to be associated with higher severity and mortality in these patients. However, autoimmune diseases were not an independent prognostic factor<sup>10,11</sup>. NLR levels remained significantly higher in the deceased group. Similar to our study; Seyit M et al. found that NLR levels were higher in COVID-19 patients in their study and Yang et al. reported NLR levels were significantly higher in severe patients<sup>12,13</sup>. In our study, patients with thrombocyte levels above  $193.5 \times 10^9/L$  had an increased risk of mortality in contrast to our study, some studies revealed a correlation between thrombocytopenia and disease severity, also mortality<sup>14</sup>.

### ***Conclusion***

We found that NLR and platelet levels are independent risk factors for mortality in patients with autoimmune disease, independent of the development of thrombocytopenia, unlike the normal population diagnosed with COVID-19.

Our study had several limitations. Firstly, we had a small sample size. In addition, autoimmune disease activity in these patients and the effect of treatments used for the disease were not included in the study. Therefore, comprehensive studies should be conducted in a larger cohorts by evaluating disease activity and treatment regimens.

**Table 1.** Comparative clinical and laboratory characteristics

Parameters	Overall population N=125	Deceased group N=30	Survivor group N=95	P value
Age, years (mean ± SD)	63.34 ± 13.95	70.00 ± 9.51	61.24 ± 14.50	<0.001
Gender				0.334
Female	72 (57.6%)	15 (50.0%)	57 (60.0%)	0.334
Male	53 (42.4%)	15 (50.0%)	38 (40.0%)	0.334
Comorbidity (other than rheumatic disease)				
Coronary artery disease	39 (31.2%)	13 (43.3%)	26 (27.4%)	0.100
Hypertension	78 (62.4%)	22 (73.3%)	56 (58.9%)	0.156
Diabetes mellitus	40 (32%)	17 (56.7%)	23 (24.2%)	0.001
Other	62 (49.6%)	20 (66.7%)	42 (44.2%)	0.032
Typical involvement on CT	103 (82.4%)	30 (100%)	73 (76.8%)	0.004
Intensive care unit admission	43 (34.4%)	27 (90%)	16 (16.8%)	<0.001
Length of stay (days)	11 (7-17.5)	16 (8-26)	10 (7-16)	0.046
Mortality	30 (24.0%)	-	-	-
Laboratory findings* (24th hour)				
White blood cell (10 <sup>9</sup> /L)	5.92 (4.26-8.37)	8.71 (5.22-10.54)	5.69 (4.11-7.64)	0.001
Neutrophil (10 <sup>9</sup> /L)	4.58 (2.47-6.95)	7.41 (3.97-9.42)	3.78 (2.31-5.97)	<0.001
Lymphocyte (10 <sup>9</sup> /L)	0.87 (0.55-1.25)	0.66 (0.4-0.95)	0.9 (0.61-1.28)	0.015
Neutrophil lymphocyte ratio	5.11 (2.46-9.72)	8.73 (4.72-19.34)	4.25 (1.94-8.17)	<0.001
Hemoglobin (g/dL)	12.53 ± 1.92	12.22 ± 2.00	12.63 ± 1.90	0.319
Platelet (10 <sup>9</sup> /L)	217.60 ± 88.28	251.77 ± 101.25	206.81 ± 81.42	0.014
C- reactive protein (mg/L)	43 (14.5-127)	112.5 (41.25-179)	33 (10-84)	<0.001
Procalcitonin (µg/L)	0.06 (0.03-0.2)	0.19 (0.08-0.74)	0.05 (0.03-0.12)	<0.001
Lactate dehydrogenase (U/L)	336 (259.5-481)	503.5 (306.5-623.5)	324 (242-406)	<0.001
Fibrinogen (g/L)	4.65 ± 1.76	5.53 ± 1.92	4.38 ± 1.63	0.002
D-dimer (mg/L)	0.8 (0.42-1.7)	1.23 (0.69-2.55)	0.75 (0.4-1.2)	0.002
Ferritin (µg/L)	277 (121-594.5)	469 (259-1218.5)	218 (110-499)	0.001

**Table 2.** Comparative autoimmune disease characteristics in deceased and survivor

Parameters	Overall population N=125	Deceased group N=30	Survivor group N=95	P value
Hashimoto's thyroiditis	33 (26.4%)	9 (30%)	24 (25.3%)	0.608
Connective tissue disease				
Rheumatoid arthritis	39 (31.2%)	11 (36.7%)	28 (29.5%)	0.459
Sjogren's syndrome	5 (4%)	2 (6.7%)	3 (3.2%)	0.593
Systemic lupus erythematosus	3 (2.4%)	-	3 (3.2%)	1.000
Scleroderma	2 (1.6%)	2 (6.7%)	-	0.056
Dermatomyositis	1 (0.8%)	-	1 (1.1%)	1.000
Other				
Behcet's disease	5 (4%)	-	5 (5.3%)	0.336
Ankylosing spondylitis	7 (5.6%)	1 (3.3%)	6 (6.3%)	1.000
Familial mediterranean fever	4 (3.2%)	2 (6.7%)	2 (2.1%)	0.243
Multiple sclerosis	4 (3.2%)	-	4 (4.2%)	0.572
Immune thrombocytopenic purpura	3 (2.4%)	2 (6.7%)	1 (1.1%)	0.143
Inflammatory bowel disease	11 (8.8%)	3 (10%)	8 (8.4%)	0.724
Psoriasis	7 (5.6%)	1 (3.3%)	6 (6.3%)	1.000
Celiac disease	1 (0.8%)	-	1 (1.1%)	1.000
Sarcoidosis	1 (0.8%)	-	1 (1.1%)	1.000
Immunoglobulin A nephropathy	1 (0.8%)	-	1 (1.1%)	1.000
Primary sclerosing cholangitis	2 (1.6%)	-	2 (2.1%)	1.000
Primary biliary cholangitis	1 (0.8%)	-	1 (1.1%)	1.000
Antiphospholipid antibody syndrome	1 (0.8%)	-	1 (1.1%)	1.000
Myasthenia gravis	6 (4.8%)	2 (6.7%)	4 (4.2%)	0.629
Guillain-barre syndrome	1 (0.8%)	-	1 (1.1%)	1.000
Pemphigus vulgaris	1 (0.8%)	-	1 (1.1%)	1.000
Immunosuppressive drug use				
Prednisolone	30 (24%)	6 (20%)	24 (25.3%)	0.556
Hydroxychloroquine	22 (17.6%)	6 (20%)	16 (16.8%)	0.692
Sulphasalazine	7 (5.6%)	3 (10%)	4 (4.2%)	0.357
Methotrexate	12 (9.6%)	4 (13.3%)	8 (8.4%)	0.480
Leflunomide	7 (5.6%)	2 (6.7%)	5 (5.3%)	0.673
Azathioprine	9 (7.2%)	3 (10%)	6 (6.3%)	0.447
Mycophenolate	5 (4%)	1 (3.3%)	4 (4.2%)	1.000
Calcineurin_inh	4 (3.2%)	1 (3.3%)	3 (3.2%)	1.000
Colchicine	7 (5.6%)	1 (3.3%)	6 (6.3%)	1.000
Biological agent	4 (5%)	1 (3.3%)	4 (4.2%)	1.000
Rituximab	1 (0.8%)	-	1 (1.1%)	1.000

**Table 3.** Univariate and multivariate regression analysis for mortality

Parameters	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.053 (1.017-1.090)	0.004		
Diabetes mellitus	4.094 (1.730-9.687)	0.001	7.435 (2.540-21.759)	<0.001
White blood cell (10 <sup>9</sup> /L)	1.179 (1.049-1.326)	0.006		
Neutrophil (10 <sup>9</sup> /L)	1.328 (1.145-1.540)	<0.001		
Lymphocyte (10 <sup>9</sup> /L)	0.851 (0.506-1.431)	0.543		
Neutrophil lymphocyte ratio	1.097 (1.042-1.155)	<0.001	1.102 (1.045-1.163)	<0.001
Hemoglobin (g/dL)	0.895 (0.721-1.112)	0.317		
Platelet (10 <sup>9</sup> /L)	1.006 (1.001-1.011)	0.018	1.008 (1.002-1.014)	0.008
C- reactive protein (mg/L)	1.009 (1.004-1.014)	0.001		
Procalcitonin (µg/L)	1.084 (0.914-1.286)	0.354		
Lactate dehydrogenase (U/L)	1.001 (1.000-1.002)	0.073		
Fibrinogen (g/L)	1.449 (1.137-1.847)	0.003		
D-dimer (mg/L)	1.048 (0.910-1.206)	0.518		
Ferritin (µg/L)	1.001 (1.000-1.001)	0.031		

**Table 4.** Predictive values of independent risk factors for mortality

Parameters	Cut-off value	Number (%) of patients*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR (95% CI)
Diabetes mellitus	-	40 (32.0)	56.7	75.8	42.5	84.7	4.1 (1.7-9.7)
Neutrophil lymphocyte ratio	7.2	44 (35.2)	63.3	73.7	43.2	86.4	4.8 (2.0-11.5)
Platelet	193.5 10 <sup>9</sup> /L	70 (56.0)	80.0	51.6	34.3	89.1	4.3 (1.6-11.4)

\*Number (%) of patients above or below the given cut-off values.  
 Abbreviations: PPV; Positive predictive value, NPV; Negative predictive value, OR; Odds ratio, CI; confidence interval.



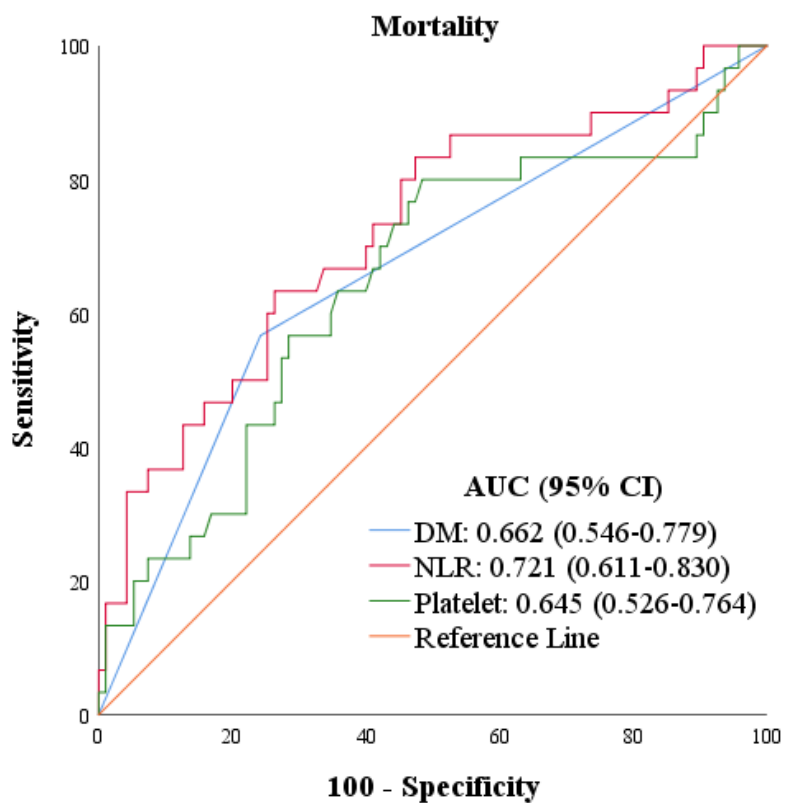


Figure 1. The AUC of DM, NLR and platelet for mortality

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## Coexistence of Brucellosis and Mushrooms Intoxication in a Patient Presenting with Toxic Hepatitis

Adem Çağlayan<sup>1</sup>, Oğuzhan Zengin<sup>1</sup>, Enes Seyda Şahiner<sup>1</sup>

<sup>1</sup> Department of Internal Medicine, Ankara City Hospital, Ankara, Turkey

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### ABSTRACT

#### *Introduction*

Elevated liver enzymes are a laboratory finding that we frequently encounter, especially in patients who apply to the internal medicine outpatient clinic with complaints of nausea, vomiting and abdominal pain. When the etiological reasons are examined in patients living in rural areas in our country, it is understood that liver enzyme elevations due to mushroom eating and consumption of raw milk products are seen more.

Coexistence of rare brucella and mushroom poisoning will be explained in our case.

## ***Introduction***

Elevated liver enzymes are a common concern at internal medical clinics. Paracetamol intoxication is one of the most frequent causes of enzyme elevation. In our country, especially in rural areas, mushrooms intoxication is also an important etiological factor <sup>1</sup>. Brucellosis is among the most common causes of zoonosis in the world. In rare cases, it may result in hepatic enzymes elevated <sup>2</sup>. We present a rare case who presented with a history of eating mushrooms and accompanied by brucella.

## ***Case Presentation***

A 50-year-old female patient was admitted to the hospital with nausea, fatigue, anorexia, headache after eating mushrooms. In addition, we learned that family members applied to the hospital with the suspicion of mushroom poisoning. The patient was conscious and vital functions were stable. On physical examination, abdominal palpation was normal. Complete blood count (CBC) revealed neutropenia and thrombocytopenia. Peripheral smear was compatible with CBC. Liver function tests were found to be high (other parameters are summarized in Table). The patient was evaluated with hepatobiliary, Portal Doppler Ultrasonography and contrast-enhanced abdominal tomography. In her imaging, the liver size was increased, diffuse density loss secondary to steatosis, and a millimetric calcific focus in the subcapsular region at the level of liver segment 8, was observed (Figure). It was observed that the increase in liver enzymes continued and the patient has vomiting. Oral intake was stopped and then intravenous hydration was started. It was learned that the patient lived in the village and was engaged in ovine breeding. It was also determined that take part of birth small cattle and consumed cheese made from raw milk. It was revealed that she had severe back, joint and headache complaints about a week ago.

A sero-agglutination test Rose Bengal was reported as weakly positive at a titer of 1:160. Rifampicin and doxycycline were administered. A significant decrease in liver enzymes was observed on the first day after treatment. In the follow-ups, liver enzyme levels regressed. When these results were assessed together, it was thought that liver enzyme elevation developed secondary to *Brucella* infection.



Figure: Contrast-enhanced abdominal tomography

Laboratories	Day 14	Day 10	Day 9	Day 7	Day 6	Day 4	Day 2	At Presentation	References
Glucose	75	103	93	112	86	76	79	108	70-99 mg/dl
Urea	36	38		29	12	19	23	32	19-49 mg/dl
Creatinine	0.64	0.67	0.54	0.49	0.34	0.40	0.48	0.59	0.5-1.1 mg/dl
Albumin	40.59	37.71	37.40	37.48	38.38	37.95	37.15	41.75	32-48 gr/L
ALP	107	123	158	178	180	176	186	235	53-141 U/L
ALT	66	137	349	412	458	481	490	346	<50 U/L
AST	24	45	310	456	560	791	928	748	<35 U/L
GGT	49	61	94	113	121	165	98	58	<38 U/L
LDH	220	232	293	372	362	379	525	607	120-246 U/L
CK	46		47		45		169	766	33-211 U/L
Total Bilirubine	0.50	0.40	1.015	1.325	1.80	1.50	0.80	0.493	0.3-1.2 mg/dL
Direct Bilirubine	0.26	0.22	0.657	0.649	0.90	0.67	0.30	0.180	<0.3 mg/dL
Sodium	145	139	139.8	138.1	136	136	139	139.0	132-146 mEq/L
Potassium	4.80	4.03	3.5	3.6	3.38	2.96	3.41	3.7	3.5-5.5 mEq/L
Calcium	8.67	8.71	8.29	8.34	8.70	8.49	8.80	8.47	8.7-10.4 mg/dL
Clorine		103	106	106	101	103	103	104	99-109 mEq/L
Hemoglobin	11.9	12.3	12.5	13.4	13.3		14.1	13.6	12-15.6 g/dL
Hematocrit	36.4	37.4	38	40.7	40	40	43.1	44.2	35-45 %
Leukocytes	5.82	5.34	4.70	4.98	4.95		3.75	3.08	3.9-10.2 x10 <sup>9</sup> /L
Neutrophils	2.57	2.09	2.04	2.61	2.61		1.59	1.03	1.5-7.7 x10 <sup>9</sup> /L
Platelets	202	263	240	245	221		127	107	150-450 x10 <sup>9</sup> /L
INR					1.11	1.13	1.00	1.04	

Table: Laboratory results of the patient

(ALP alanine aminotransferase, AST aspartate aminotransferase, GGT gamma-glutamyltransferase, INR international normalized ratio, CK creatinine kinase, LDH lactate dehydrogenase)

### Discussion

There are many different etiological factors that cause liver dysfunction. Mushroom poisoning, which can lead to liver failure and death, is one of the most important causes. It is reported that the cause of death of more than 90% of patients with mushroom poisoning is acute liver failure<sup>3</sup>. Usually the first symptoms are associated with the gastrointestinal tract. Liver dysfunction is seen in the late stage. Detection of amatoxins by ELISA (enzyme-linked immunosorbent test) may be useful in early diagnosis<sup>4</sup>. Medical history plays an extremely critical role in early diagnosis and treatment.

Numerous infectious agents, although rare, can cause acute liver dysfunction. Brucella is not primary hepatotropic, but it can cause liver enzyme elevation. Organ involvement is observed in approximately 30% of disease. Anemia, leukopenia and thrombocytopenia may be occurred due to hematologic system damaged. In addition, hepatic or splenic abscesses accompanied by elevated transaminase can be detected. Moderate hepatosplenomegaly, and sometimes acute hepatitis may develop. Acute hepatic failure is observed very rarely when an underlying etiological factor is present<sup>5</sup>.

In this case, viral hepatitis, vascular events and autoimmune disease were considered in the differential diagnosis. When epidemiological, demographic, clinical features, laboratory findings and diagnostic imaging were evaluated together, these diagnoses were ruled out. Mushroom intoxication and brucellosis were considered in the differential diagnosis with the results obtained. Fungal intoxication could not be clearly excluded in the diagnosis due to amatoxin analysis could not be performed and intoxication was suspected in family members. Since the sero-agglutination test Rose Bengal was weakly positive and the patient responded to antibiotherapy, liver enzyme dysfunction caused by brucella was considered in the diagnosis.

### ***Conclusion***

In patients presenting with a history of eating mushrooms, it is very important to keep in mind other rare causes that may cause liver dysfunction apart from intoxication.

### ***Declaration***

The authors have no conflicts of interest to declare.



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## Pineal Gland Germinoma And Pituitary Insufficiency Presenting With Weight Loss

Emine Sena Sözen<sup>1</sup>, Oğuzhan Zengin<sup>1</sup>, Enes Seyda Şahiner<sup>1</sup>

<sup>1</sup> Department of Internal Medicine, Ankara City Hospital, Ankara, Turkey

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### ABSTRACT

#### *Introduction*

Intracranial germinomas are rare cancers that primarily affect pediatric age group patients making them rarer still in adults. This report presents a case of a primary intracranial germinoma arising in the pineal region of a 24 year old male. The patient presented with a history of weight loss and progressive vision loss secondary to obstructive hydrocephalus. MRI demonstrated a large enhancing mass lesion in the region of the pineal gland with radiological features suggestive of a germinoma. Immunohistochemical stains confirmed the histological diagnosis, with positive staining for C-Kit, OCT4 and PLAP. In summary, this case report highlights that the diagnosis of pineal gland germinoma present in a young male is made by immunohistochemistry and detailed physical examination.

Correspondence Address: Emine Sena Sözen University District 1604. Street No: 9 Çankaya / Ankara

E-posta: [senasozen7@gmail.com](mailto:senasozen7@gmail.com)

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## ***Introduction***

Hypopituitarism is the name given to clinical syndromes that develop as a result of the insufficiency of one or more hormones produced in the anterior pituitary gland <sup>1</sup>. Intracranial germ cell tumors (IGCT) are more common in males and approximately 50% are located in the pineal gland. IGCT are divided into two main groups, pure germinoma and nongerminomatous germ cell tumors (NGGCTs). Germinoma is the most common subtype, accounting for over two thirds of all IGCTs <sup>2</sup>.

## ***Case***

A 24-year-old male patient with an unremarkable past medical history presents to the clinic with complaints of loss of appetite and fatigue that started about a year ago. The patient was previously investigated for malignancy in a different center, and no pathology was detected in the thorax and abdominal tomography. He lost approximately 20 kg in the last year. The patient had no history of drug, herbal or substance use. On physical examination, he was 170 cm tall, weighed 40 kilograms. His body mass index was 13.85 kg/m<sup>2</sup>. Decreased visual acuity, limitation of eye movements, bilateral decreased testicular volume were detected.

Pituitary hormones were requested from the patient with the preliminary diagnosis of panhypopituitarism. Hormone tests requested from the patient as followed:

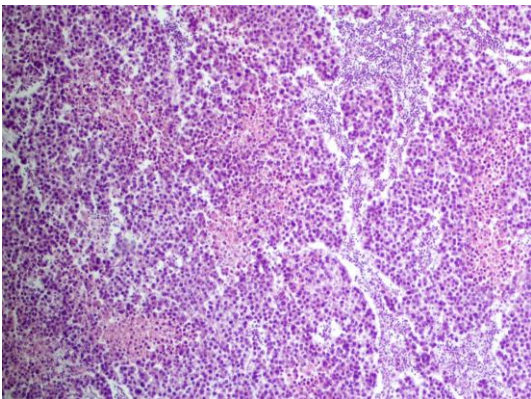
TSH 1.39 mU/L(N:0.27-4.2), fT4 0.56 ng/dl (N:0.89 - 1.76), fT3 2.17 ng/L(N:2, 3 - 4.2), Prolactin 70.4 µg/L(N:2.1 - 17.7),Growth Hormone (GH) 4.6 µg/L(N: 0.05 - 3),IGF-1 (Insulin Like Growth Factor 1) 72 µg/L (N:116 - 358),ACTH 11.1 pg/mL (N:0-100),Cortisol 1.8 µg/dL (N:5.2-22.4),FSH 1.9 U/L (N:1.4 - 18.1),LH 0.5 U/L (N:1.5 - 9.3),Total Testosterone <0.07ug/L (N:1, 64 - 7.53)

Other laboratory tests were found to be normal.

Pituitary magnetic resonance imaging was requested from the patient. A 27.5x27x25 mm mass infiltrating the pituitary gland in the posterior part of the pineal gland localization causing significant compression on the Aquaductus Sylvii and triventricular obstructive hydrocephalus, was detected invading the optic chiasm.



**Fig 1: A mass lesion of 27.5x27x25 mm in the localization of the pineal gland**



**Fig 2: Intraoperative material strong staining with PLAP**

### *Discussion*

Intracranial germ cell tumors are rare neoplasms. Joint involvement of the suprasellar region and the pituitary gland is rare 3. Prognosis is worse in such cases. In the advanced age group, it should be considered that pineal gland germinoma accompanies the pituitary insufficiency, although it is rare. We wanted to emphasize the importance of detailed physical examination to help in the diagnosis in patients presenting with weight loss if no pathology is detected on initial imaging. As a result of the examinations of our patient who was hospitalized for weight loss, coexistence of pituitary insufficiency and pineal gland germinoma was detected.

In the literature, pituitary and suprasellar involvement is rarely seen in patients with pineal gland germinoma. Our case had pituitary and suprasellar involvement. In cases presenting with weight loss and deterioration in visual acuity, pituitary insufficiency should be considered in the preliminary diagnosis.

### ***Declaration***

The authors have no conflicts of interest to declare.

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