CASE REPORT

Extranodal NK/T-cell lymphoma, nasal type with cutaneous involvement – a rare case associated with chronic C hepatitis and occupational metal dust exposure

EUGEN HORATIU STEFANESCU1), NICOLAE CONSTANTIN BALICA1), IOANA DELIA HORHAT1), FLAVIA BADERCA2), MARIUS OCTAVIAN PRICEP3), HORATIU CONSTANTIN URECHESCU3), DANIEL FLORIN LIGHEZAN2), CRISTIAN ANDREI SARAU4)

1)Department of ENT, “Victor Babeș” University of Medicine and Pharmacy, Timisoara, Romania
2)Department of Microscopic Morphology, “Victor Babeș” University of Medicine and Pharmacy, Timisoara, Romania
3)Department of Maxillofacial Surgery, “Victor Babeș” University of Medicine and Pharmacy, Timisoara, Romania
4)Department of Cardiology, “Victor Babeș” University of Medicine and Pharmacy, Timisoara, Romania

Abstract
Extranodal natural killer (NK)/T-cell lymphomas, nasal type are rare and aggressive non-Hodgkin’s lymphomas (NHLs), with unknown etiology, rapid evolution and poor prognosis, due to midline tissue destruction and rapid spreading of the tumor. These lymphomas occur commonly in the nasal cavity and upper aerodigestive tract, but can also present involvement of the skin, salivary gland, and testis. We describe a case of nasal type T-cell NHL involving the nasal cavity and determining right thigh cutaneous metastases in a 47-year-old female associated with liver comorbidities and occupational dust exposure. The patient was suffering from chronic type C hepatitis and cirrhosis and she has been occupationally exposed to metal dust for 10 years. Clinical and laboratory investigations were performed. Essential for diagnosis and treatment protocol was nasal endoscopy and biopsy of nasal and cutaneous lesions. The histopathological exam was consistent with NK/T-cell lymphoma. Patient was diagnosed in Ann Arbor stage IVA. Chemotherapy was initiated with Bleomycin, Etoposide, Adriamycin (Doxorubicin), Cyclophosphamide, Oncovin (Vincristine), Procarbazine and Prednisone, but it was stopped after two cycles because of the liver condition. The treatment plan also included radiotherapy, but soon after initiation, the patient died because of a liver complication.

Keywords: extranodal NK/T-cell lymphoma (nasal type), cutaneous involvement, chronic C hepatitis, cirrhosis, occupational metal dust exposure.

Introduction
Non-Hodgkin’s lymphomas (NHLs) of the head and neck are rare malignancies, with higher incidence in Asia than United States and Europe [1]. In 2008, World Health Organization (WHO) updated the existing classification of lymphoid tissues tumors [2], including three aggressive mature natural killer (NK)-cell neoplasms: extranodal NK/T-cell lymphoma, nasal type [3], aggressive NK-cell leukemia [4], and chronic lymphoproliferative disorders of NK-cells [5].

NK/T-cell lymphomas are almost exclusively extranodal [6]. Extranodal NK/T-cell lymphomas are rare and aggressive malignancies that commonly occur in the nose, causing destructive midfacial necrotizing lesions and secondarily can affect other extranodal sites, lymph nodes and bone marrow. They can occasionally occur primarily in the skin, salivary gland, and testis, without an apparent nasal involvement. Extremely rare, NK/T-cell lymphoma present with primary intranodal involvement [7]. Extranodal NK/T-cell lymphomas are categorized by some authors into ‘nasal’ and ‘nasal-type’, according to the primary site of involvement [8]. Patients with lymphoma found only in the nasal area are considered to have early stage disease, and those whose lymphoma is found in other organs are considered to have advanced stage disease. However, it has been shown that most, if not all non-nasal lymphomas are associated with occult nasal primaries [1, 9–12].

NK/T-cell lymphomas present with various histopathological aspects, but frequently they consist of small, medium or large malignant lymphoid cells that show angiocentricity. Most of the tumors have large areas of necrosis [1, 7].

Therefore, of utmost importance in the diagnosis and classification of the lymphoma is the immune phenotype of malignant cells established by immunohistochemistry [13]. The nasal NK/T-cell lymphoma is a distinct clinical entity characterized by tumor cells positive for CD56, CD2, CD3 and CD45R0. A consistent association with Epstein–Barr virus (EBV) is observed, but shows geographical and racial variations [14–16]. Upon treatment, the malignant cells can lose CD56 positivity and change their morphology, even resembling normal lymphocytes, making the diagnosis of NK/T-cell lymphoma recurrences even more difficult [1].
NK/T-cell lymphomas have low overall survival rates, especially in late stages, even when proper treatment is applied.

**Aim**

We aim to present a rare case of extranodal NK/T-cell lymphoma with cutaneous involvement that was immunohistochemically negative for EBV.

**Case presentation**

We present the case of a 47-year-old female (V.E.) patient addressed to Department of Otorhinolaryngology, Emergency City Hospital, Timișoara, Romania, with sinonasal pathology, on January 2013 (Patient file No. 770 on January 8, 2013). Five years before she was diagnosed with maxillary sinusitis unsuccessfully treated with several courses of antibiotics. At hospital admission, the patient presented also three cutaneous nodules in the left thigh. She was diagnosed in 2010 with chronic C hepatitis and cirrhosis, and she had a history of occupational exposure to metal dust. Laboratory investigations included full blood count, serum biochemistry, serum lactate dehydrogenase (LDH), and hepatitis B and C virus testing. Nasal endoscopy and a contrast-enhanced computed tomography (CECT) of the sinonasal area demonstrated the presence of a tumor. In order to establish the diagnosis biopsies were performed, one from the sinonasal tumor through nasal endoscopy and one from necrotized thigh tumor. The specimens were fixed in 4% (v/v) buffered formalin, sent to the Service of Pathology of the same Hospital and embedded in paraffin. Four μm sections were cut using a semi-automated rotary microtome Leica RM2235, displayed on Super DM500 microscope and the pictures were captured through a Leica DMshare system.

For immunohistochemistry, the slides were dewaxed in toluene and rehydrated in baths with decreasing concentrations of ethanol. Heat-induced antigen retrieval was performed using a pressure cooker in a buffer bath stated on the antibody datasheet. Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide solution (Peroxidase Block Solution, Novocastra, Newcastle, UK). Sections were treated with 0.4% casein in phosphate-buffered saline (PBS), with stabilizers, surfactant, and 0.2% Bronidox L as a preservative (Novocastra, Newcastle, UK), in order to block unspecific binding and then were incubated with the primary antibodies [CD3, CD20, CD56, granzyme B, perforin, CD30, Ki67, EBV, and pan-cytokeratin (CK) AE1/AE3]. All the antibodies were obtained from Novocastra (Newcastle, UK) and the dilutions, incubation time, and antigen retrieval solutions were resumed in the Table 1. The antibodies diluent and the antigen retrieval solutions were supplied by Novocastra (Newcastle, UK). The detection system used was Novolink Polymer Detection System (Novocastra, Newcastle, UK). The antigen-antibodies complexes were visualized by 3,3’-Diaminobenzidine tetrahydrochloride (DAB, Novocastra, Newcastle, UK). The nuclei were counterstained with Hematoxylin. The slides were observed using a Leica DM500 microscope and the pictures were captured through a Leica DMshare system.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Dilution</th>
<th>Antigen retrieval</th>
<th>Incubation time</th>
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<tbody>
<tr>
<td>CD3</td>
<td>LN10</td>
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<td>30 minutes</td>
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<tr>
<td>CD56</td>
<td>MRQ42</td>
<td>1:300</td>
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<td>30 minutes</td>
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<tr>
<td>CD20</td>
<td>L26</td>
<td>1:300</td>
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<td>30 minutes</td>
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<td>Granzyme B</td>
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<td>RTU</td>
<td>Heat-induced epitope retrieval, pH 6</td>
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<tr>
<td>Perforin</td>
<td>5B10</td>
<td>1:20</td>
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<td>20 minutes</td>
</tr>
<tr>
<td>CD30</td>
<td>JCM182</td>
<td>1:100</td>
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</tr>
<tr>
<td>Ki67</td>
<td>MM1</td>
<td>1:200</td>
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<td>30 minutes</td>
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<tr>
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<td>Trypsin</td>
<td>60 minutes</td>
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<td>1:50</td>
<td>Heat-induced epitope retrieval, pH 6</td>
<td>60 minutes</td>
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Informed consent from the patient was obtained and we also obtained approval from the Ethics Committee of the “Victor Babeș” University of Medicine and Pharmacy, Timișoara for presenting this case.

The patient addressed the Department of Otorhinolaryngology, Emergency City Hospital, Timișoara, with nasal obstruction, faulty smell, headache, the midfacial skin inflammatory signs (redness, pain and swelling), bridging of the nose (Figure 1a), palpebral edema, chemosis, nasal crusts, frontal sinus fullness and poor general status. She presented nasal obstruction, faulty smell, and headache five years before current hospital admission, and she was diagnosed with chronic maxillary sinusitis and unsuccessfully treated with antibiotics. The facial and ocular symptoms occurred in February 2012. In March 2012, she also noticed a swelling on the left thigh with redness of the skin that increased in size and were covered by modified erythematous skin around the tumor. The two smaller nodules had 0.5/1 cm in size and in the cervical area was observed. On the left thigh, the necrotic tumor had 5/6 cm in size and was covered with a clean crust with inflammatory and infiltrated area around the tumor. The two smaller nodules had 0.5/1 cm in size and were covered by modified erythematous skin (Figure 1b).

As for the medical history, she was diagnosed in 2010 with chronic C hepatitis and cirrhosis. She also worked in toxic environment for 10 years (steel industry).

On clinical examination, no lymph node involvement in the cervical area was observed. On the left thigh, the necrotic tumor had 5/6 cm in size and was covered with a clean crust with inflammatory and infiltrated area around the tumor. The two smaller nodules had 0.5/1 cm in size and were covered by modified erythematous skin (Figure 1b).

Laboratory testing showed red blood cell count (RBC), hemoglobin (Hb) and hematocrit (Ht) with low values [RBC 3.25/10⁶/μL (3.8–5.3/10⁶/μL), Hb 11.2 g/dL (12–15 g/dL), Ht 33.7% (34–45%)]. The liver function tests showed poor liver function with high levels of alanine...
Extranodal NK/T-cell lymphoma, nasal type with cutaneous involvement – a rare case associated with liver involvement and chronic hepatitis C virus infection

**Laboratory findings:**
- Transaminase (ALAT) and aspartate aminotransferase (ASAT) [ALAT 97 U/L (8–65 U/L), ASAT 150 U/L (8–40 U/L)]. Serum LDH was 520 U/L (100–190 U/L). Albumin was 31 g/L, alkaline phosphatase (ALP), prothrombin time (PT)/international normalized ratio (INR) borderline, but still normal limits. Virus tests for hepatitis B were negative but were positive for hepatitis C [surface antigen of the hepatitis B virus (HBs Ag) negative, antibodies against hepatitis C virus (anti-HCV), enzyme immunoassay (EIA) positive]. Renal function was normal.
- Chest X-ray was normal. Abdominal ultrasounds were performed – as the suspicion of malignancy was raised – but no enlarged lymph nodes or other abnormalities were detected (liver and spleen size in normal limits). Negative microbiological findings ruled out infectious nature of the lesion. Syphilis was excluded by serology. Normal chest radiography and absence of renal involvement ruled out Wegener’s granulomatosis.

**Nasal endoscopy:**
- Nasal endoscopy revealed destruction of nasal septum (both cartilaginous and osseous part), partial destruction of the lateral walls of the nasal cavities, crusts in the nasopharynx and nasal cavities. When the crusts were removed, the nasal and nasopharyngeal mucosa showed granulations and the cartilaginous septum was eroded due to necrosis. The biopsy was performed from septum, and lateral nasal wall.

A CECT of the head and neck demonstrated the presence of a midline tumor with bony destruction and a mass localized in the right maxillary sinus, extending into the right sphenoid, ethmoid and frontal sinuses (Figures 2 and 3).

The necrotic lesion of the thigh was also biopsied. Both specimens were processed using the routine histological technique.

**Histopathology:**
- On HE slides, lamina propria of the nasal mucosa was infiltrated by an angiocentric and angioinvasive infiltrate of medium to large malignant lymphocytes. The respiratory epithelium was ulcerated and covered by eosinophilic necrotic detritus admixed with neutrophils. The tumor cells had moderately abundant pale pink cytoplasm and folded and indented pleomorphic nuclei. Many mitotic figures were observed in the malignant lymphocytes. Between tumor cells there were numerous extravasated erythrocytes (Figures 4–7). The cells were positive for CD3 (Figures 8 and 9), CD56 (Figure 10), and negative for CD20 (Figure 11) and pan-CK AE1/AE3 (Figures 12 and 13).

The biopsy of cutaneous lesion showed similar histopathological features. The dermis and subcutis were heavily infiltrated by medium- to large-sized malignant lymphocytes, with eosinophilic cytoplasm and pleomorphic nuclei, with typical and atypical mitosis. Between the cells, lot of nuclear debris was observed. The epidermis was ulcerated (Figures 14–17).

The cells had the same immunophenotype as the mucosal counterpart, being positive for CD3, CD56 and negative for CD20 and pan-CK AE1/AE3. On skin biopsies, we performed also granzyme B and perforin that turned out to be positive on few isolated cells. CD30 and EBV were negative. The mitotic index was highlighted using Ki67 reaction and almost all cells were positive at nuclear level (Figures 18–25).

The diagnosis was extranodal NK/T-cell lymphoma, nasal type with secondary cutaneous involvement. The Ann Arbor stage was IVA. Simultaneously, she presented nasal abscess, right pansinusitis, chronic C hepatitis, cirrhosis.

In the Department of Otorhinolaryngology, the patient underwent antibiotic, steroid, and anticoagulant treatment and after histological diagnosis was made, it was transferred to the Department of Oncology–Hematology for further treatment.

Chemotherapy was initiated with Bleomycin, Etoposide, Adriamycin (Doxorubicin), Cyclophosphamide, Oncovin (Vincristine), Procarbazine and Prednisone (BEACOPP regimen – cycles of 21 days with no drugs on days 15–21; Bleomycin 10 mg/m²; Etoposide 150 mg/m²; Adriamycin 30 mg/m²; Cyclophosphamide 750 mg/m², Oncovin 1.4 mg/m²; Procarbazine 100 mg/m²; Prednisone 40 mg/m²). The chemotherapy was stopped after two cycles because of liver condition and radiotherapy was contemplated. Planned radiotherapy involved the delivery of 50 Gy equivalents in daily fractions of 2 Gy, covering the nasal, paranasal cavities, nasopharynx, the Waldeyer’s ring and the tight region. Unfortunately, the patient died just after starting radiotherapy due to liver complication.
Figure 4 – Lamina propria filled by tumor cells, covered by pseudostratified epithelium with foci of squamous metaplasia (HE staining, ×100).

Figure 5 – Highly pleomorphic tumor cells showing many mitoses (HE staining, ×400).

Figure 6 – The medium to large sized destroyed the ductal and acinar component of nasal mucosa (HE staining, ×400).

Figure 7 – Between highly pleomorphic tumor cells, lot of nuclear debris was observed (HE staining, ×400).

Figure 8 – Tumors cells positive for CD3 were observed in the nasal lamina propria and infiltrating nasal mucosa with foci of squamous metaplasia (Anti-CD3 antibody immunostaining, ×400).

Figure 9 – Malignant pleomorphic lymphocytes were positive for CD3 (Anti-CD3 antibody immunostaining, ×400).
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Figure 10 – Intense cytoplasmic positivity for CD56 in all of tumor cell (Anti-CD56 antibody immunostaining, ×400).

Figure 11 – Between highly pleomorphic tumor cells few lymphocytes were positive for CD20 (Anti-CD20 antibody immunostaining, ×400).

Figure 12 – Tumor cells were negative for pan-CK AE1/AE3 (Anti-pan-CK AE1/AE3 antibody immunostaining, ×400).

Figure 13 – Squamous epithelium from foci of metaplasia was positive for pan-CK AE1/AE3, whereas the tumor cells were negative (Anti-pan-CK AE1/AE3 antibody immunostaining, ×400).

Figure 14 – Tumors cells were observed in the all level of the dermis and were infiltrated adipose tissue (HE staining, ×400).

Figure 15 – Malignant pleomorphic lymphocytes and many extravasated erythrocytes (HE staining, ×400).
Figure 16 – The epidermis was ulcerated and covered with acidophilic fibrin and necrotic debris (HE staining, ×400).

Figure 17 – Highly pleomorphic tumor cells with big, vesicular nuclei and prominent nucleoli (HE staining, ×400).

Figure 18 – Tumor cells were positive for CD3 (Anti-CD3 antibody immunostaining, ×400).

Figure 19 – Malignant lymphocytes positive for CD56 (Anti-CD56 antibody immunostaining, ×400).

Figure 20 – Few tumor cells were positive for granzyme B (Anti-granzyme B antibody immunostaining, ×100).

Figure 21 – Malignant pleomorphic lymphocytes were positive for perforin (Anti-perforin antibody immunostaining, ×100).
Extranodal NK/T-cell lymphomas have a unique clinical course. They usually appear in middle-aged male patients with good status despite their advanced disease and presence of B-symptoms (fever, night sweats, weight loss), in contrast with this case where the patient was a female in a bad general condition probably due to the liver comorbidities [8]. The B-symptoms were present in our case as well.

As in our case, cutaneous involvement in NK/T-cell lymphoma appears frequently in the course of primary nasal lymphomas [8]. In more than two-thirds of patients, the cutaneous lesion is represented by facial cellulitis or leg ulcer [8, 17]. A non-healing leg ulcer or facial cellulitis should aware dermatologists on the existence of cutaneous lymphoma.

Accurate diagnosis and staging are of paramount importance for treatment. Biopsy is essential for diagnosis. Extensive necrosis can make histological diagnosis difficult, so we need to obtain biopsy specimens as large as possible. The immunohistochemical profile is typical, CD3 and CD56 are positive. EBV reaction is usually positive, but there were described cases, like ours, where EBV-testing is negative. If available, granzyme B and perforin could be performed, tumor cells being positive to these markers.

In our Department, a nasal endoscopy is routinely performed in any nasal pathology and biopsy specimens are taken from suspicious lesions. A high degree of suspicion is necessary in every nasal lesion that has no improvement following correct treatment.

There are several commonly encountered associations like NHL and hepatitis B or NHL and occupational exposures.

As hepatitis B virus carrier rates are high in patient with NK/T-cell lymphoma, hepatitis B virus testing was performed as routine [18], but in our case was negative. Our patient instead was known with chronic C hepatitis (positive testing) and cirrhosis. There are no other papers in English literature that presents a coexistence of hepatitis C and NK/T-cell lymphoma.

Moreover, it is well-known the association between NHL and several occupations. The capacity of different occupational exposures as pesticides, dusts (metal, wood, paper), paints, diesel exhaust fumes, cleaning fluids,
cutting oils and solvents, to produce NHL was studied by some authors [19]. They demonstrated that exposure to metal dusts could represent an increased risk to developing NHL. Our patient worked in toxic environment (steel industry for approximately 10 years).

Most of the patients are diagnosed with advanced disease and accurate staging is very important in the management of this cases. Staging investigations include full blood count, serum biochemistry, LDH, nasal endoscopy, CT scan of the head, chest and abdomen, and bilateral bone marrow biopsies. NK/T-cell lymphomas are 18-fluorodeoxyglucose avid [9, 10] and positron-emission tomography (PET)/CT is the recommended imaging modality. When PET/CT is unavailable, CT or magnetic resonance imaging (MRI) may be acceptable [20]. In nasal lesions, careful initial imaging is imperative for accurate planning of subsequent radiotherapy. Chest X-ray and abdominal ultrasound are acceptable methods for monitoring the involvement of the lungs, liver and spleen.

Ann Arbor Classification (with Cotswolds modifications) is still the most used to evaluate the cases of NHL, but makes no distinction between primary nodal and primary extranodal lymphomas. Besides, as opposite to Hodgkin’s lymphoma, most patients with NHL have advanced and extranodal disease with more than 50% of patients with NK/T-cell lymphomas diagnosed (as in our case) in advanced stages (III or IV) [8]. The Ann Arbor system also fails to identify the aggressive subgroups that spread to discontinuous lymph nodes and extranodal sites [21, 22].

Extranodal NK/T-cell lymphoma is both chemosensitive and radiosensitive.

For localized disease, radiotherapy combined with chemotherapy is the standard approach [6, 12, 20]. There is no clear evidence that concomitant radiotherapy and chemotherapy is necessary because sequential chemotherapy and radiotherapy seems to have comparable results and are better tolerated. Cyclophosphamide, Hydrox daunorubicin (also called Doxorubicin or Adriamycin), Oncovin (Vincristine), Prednisone, also known as CHOP-based chemotherapy even if followed by radiotherapy is not recommended for NK/T-cell lymphoma, as the complete remission rate is less than 60%, with a three-year overall survival of 59% [23].

The mainstay of treatment for advanced-stage, relapsed or refractory NK/T-cell lymphoma is a combination of chemotherapy and radiotherapy. Chemotherapy generally requires multiple (4–6) repeated cycles of multiple-agent chemotherapy. Cycles are given every 3–4 weeks. BEACOPP is the usual treatment. L-asparaginase as a single agent was found to be effective for relapsed/refractory NK/T-cell lymphomas and can be also included in a more effective regimen – SMILE (Dexamethasone, Methotrexate, Ifosfamide, L-asparaginase, Etoposide) and is considered to be better than BEACOPP but only hematopoietic stem cell transplantation (HSCT) is expected to be curative in advanced cases [24].

The outcome of T-cell lymphoma is unfavorable when compared to B-cell lymphoma, and the outcome of NK-cell lymphoma is even worse [25–28].

Several risk factors have been identified for NK/T-cell lymphomas. Some authors try to subdivide NK/T-cell lymphoma in nasal and nasal-type, according to the primary site of occurrence. Even if the morphological and immunohistochemical histopathological aspects of these two entities are similar, it seems that the prognosis differs from one category to the other, the ‘nasal’ group being less aggressive [8]. Many authors tried to identify prognostic factors for NK/T-cell lymphoma, but only performance status and liver involvement appeared to have impact on survival rate [8, 29–36].

In one study, 90% of ‘nasal’ NK/T-cell lymphomas were limited to one anatomical site whereas ‘nasal-type’ counterpart affected two or more anatomical sites, as in our case [8]. In the same paper and similar to our case, B-symptoms, cytopenia and International Prognostic Index (IPI) were more often found in the patient with ‘nasal-type’ variant of NK/T-cell lymphoma [8].

Patients in stage IIIE/IV are present more aggressive tumor behavior and poorer prognosis compared with patients in stage IE/IIIE [37]. The extent of nasal lymphoma was considered as a prognostic factor in a few studies [38, 39], and it was defined as bony invasion or septum perforation and invasion of the skin – both occurred in our patient.

A retrospective analysis of 172 patients with NK/T-cell lymphoma and aggressive NK-cell leukemia identified non-nasal disease, stage, performance status, and numbers of extranodal sites to be significant prognostic factors [40].

## Conclusions

This paper presented an interesting case of extranodal NK/T-cell lymphoma of nasal cavity with cutaneous secondary involvement that appeared in association with chronic C hepatitis and after occupational exposure at metal dust. Moreover, the paper highlighted a rare case of extranodal NK/T-cell lymphoma, positive for CD3, CD56, granulyme B and perforin, but negative for EBV, an immune phenotype that represents less than 3% of extranodal NK/T-cell lymphoma.

## Conflict of interests

The authors declare that they have no conflict of interests.

## References


**Corresponding author**
Flavia Baderca, Associate Professor, MD, PhD, Department of Microscopic Morphology, “Victor Babeș” University of Medicine and Pharmacy, 1A Eftimie Murgu Square, 300154 Timișoara, Romania; Phone +40256–204 907, Fax +40256–204 900, e-mail: flaviabaderca@gmail.com

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