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BILATERAL ENLARGEMENT OF MAJOR SALIVARY GLANDS AS AN INITIAL SIGN OF ACUTE MYELOID LEUKEMIA: CASE REPOT

БИЛАТЕРАЛНО ОТЕКУВАЊЕ НА ГОЛЕМИТЕ САЛИВАРНИ ЖЛЕЗДИ КАКО ИНИЦИЈАЛЕН СИМПТОМ КАЈ АКУТНА МИЕЛОИДНА ЛЕУКЕМИЈА

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Abstract

There is a wide spectrum of causes of bilateral enlargement of submandibular and parotid salivary glands. Usually, these enlargements may be due to viral, metabolic, systemic or medication nature. Part of these pathologic conditions may be easily diagnosed based on the clinical presentation and thorough anamnesis. The non-differentiated bilateral enlargements may be a huge challenge for the diagnostic process, where a deep knowledge of the possible etiology for such condition is required, as well as physician experience and aptitude for differential diagnostics. This case report is about the bilateral enlargement of submandibular and parotid glands, as initial sign in acute myeloid leukemia (AML). **Keywords:** salivary glands, acute myeloid leukemia, non-Hodgkin lymphoma, leukemia.

Апстракт

Постои широк спектар на причини за билатерално зголемување на субмандибуларните, односно на паротидните саливарни жлезди. Најчесто овие отекувања може да бидат од вирусна, метаболичка, системска или медикаментозна природа. Дел од ваквите патолошки состојби можат лесно да се дијагностицираат преку клиничка слика и добра анамнеза, додека за неиздиференцираните билатерални отекувања, поставувањето на дефинитивна дијагноза е голем предизвик и бара познавање на сета можна етиологија која би можела да доведе до ваква состојба, како и поседување на искуство и вештина на терапевтот во диференцијалната дијагностика. Овој приказ на случај се однесува на билатерално зголемување на субмандбуларните, односно паротидни жлезди, како иницијален знак за акутна миелоидна леукемија (АМЛ). **Клучни зборови:** саливарни жлезди, акутна миелоидна леукемија, нон-Хоџкин лимфом, леукемија.

Introduction

Acute myeloid leukemia (AML) in general is a disease that occurs in older-age patients; AML rarely appears in patients under the age of 4. The mean age of patients who suffer from this disease is 63. Although there is no known precise etiology, there are cases of AML occurring after radiotherapy, exposure to some chemical (genotoxic) factors or medication treatment (especially if it is associated with an existing hematological disease). In the basis of the pathogenesis of this disease lays malignant transformation of multipotent, hematopoetic stem cells, due to genomic alterations (mutations of genes and chromosomal inversions, as well as translocations). An enlargement of parotid and submandibular glands, with no other clinical symptoms, is a rarity in the initial manifestation of AML. The physician should be prepared for this unusual presentation of the disease, because any postponement of the diagnostic process may be fatal. The aim of this case report is to emphasize the importance of correct and timely diagnostics of AML in a patient with unusual initial presentation.

Case report

A female 26-year-old patient, a physician, was referred to the Clinic for Maxillofacial Surgery in Skopje in September 2016, with bilateral enlargement of submandibular glands, which were painless and soft on palpation. The enlargement had persisted for 8 days. On the first examination she provided an already done ultra-

sonographic analysis, which was in favor of infective mononucleosis with enlarged lymph nodes bilaterally, in the submandibular area. Routine laboratory analyses were performed, a complete blood analysis and differential blood analysis, including CRP and sedimentation. They were in normal range (WBC : 6.9 X 10^9/L, RBC: 4.29 X 10^12/L PLT 269 X 10^9/L). Serum analysis was also performed, for a potential virus infection (CMV, MUMPSs and EBV), all with negative outcome. In the peripheral blood smear analysis, the percentage of lymphocytes were 59,3% (22-35%). Non-segmented neutrophils were found to be 3,3% (2-5%), segmented 28,6% (58-68%) and monocytes 8,8% (4-8%). The patient was referred to the Clinic for Hematology, where she was advised to perform a fine-needle aspiration biopsy (FNAB) of the submandibular glands. The cytological analysis revealed a chronic inflammation, i.e. hyperplastic ductal epithelium, with no cytological atypia. She had been treated with proteolytic enzyme in the form of a supplement (Serrapeptase) and cephalosporine antibiotics – cefixime (Pancef), then with ciprofloxacin (Citeral), along with anti-swelling treatment (Chymoral forte). Two weeks later, the patient complained about strong pain in the submandibular area, and increased body temperature of 38°C (intermittent, every 3-4 days). At the same time, the submandibular glands started to become palpable, on the right side with a dimension of a walnut, and on the left side with a dimension of an egg, tender and slightly painful. No other lymph nodes were palpable in the neck area. Following worsening of the symptoms, 50 days after the onset, the patient was hospitalized in the Clinic for maxillofacial surgery for a period of 6 days. Antibiotic and antiphlogistic treatment was given. The blood test results were within the normal ranges and did not correspond with the clinical presentation (WBC: 4.0 X 10^9/L, RBC : 5.39 X 10^12/l , PLT 180 X 10^9 /L). A stroboscopic examination was performed at the Clinic for otorhinolaryngology, with a normal appearance of the larynx (oropharyngoscopically the left tonsil was with cripts and detritus). Serologic tests were performed for a possible tularemia – with a negative finding. The findings from the Clinic for rheumatology were also negative and did not indicate a presence of lymphoepithelial lesion of the salivary glands (Sy, Sjogren, M. Mikulicz). HBsAgQ2 and Anti-HCV were also negative, after which she was referred to perform an MRI. The radiology report was as follows: in the projection of the left submandibular gland there is an incapsulated change with a dimension of 28x21 mm, with a signal in favor of a hemorrhage. This change might have been an inflammatory haematoma in phase of organization, taking into consideration the pointed inflammatory reaction of the surrounding deep fat tissue in the submandibular area, as well as the presence of an increased number of reactive lymph nodes in the region. A smaller haematoma was observed in the right submandibular gland, with dimensions of 25x11 mm, with no presence of pathologically colored capsule. Both parotid and thyroid glands were with normal appearance. On the 51st day of the onset of symptoms, the serologic analysis revealed a positive value for EBV: (EBNA)IgM 0,57 (grey zone). The examination performed at the Institute for lung diseases and tuberculosis ruled out tuberculosis as a possible cause for the condition. After 3,5 months of the onset of symptoms, both parotid glands got enlarged. A serologic test for EBV presence was again performed, with negative values, but with present leukocytosis: Le 13.00 x10^9/L (4.0-11.0), [Lymf 48.80% (25-40 %) and Mon 34.40 % (3.0-7.0 %). Because of the bilateral enlargement of parotid glands, the patients was again referred to the Clinic for rheumatology, where all test results were negative. Two days after the confirmed leukocytosis, in the axillary area, a palpable painless lymph node was observed, associated with subjective feeling of excessive sweating. Tests were performed at the Clinic for infective diseases and febrile conditions with ELFA, and a positive value for EBV IgM-1,0 was found, with increasing value five days later (EBV IgM: 1,53). Four months after the onset of symptoms, a sternal punction was performed and the following results were found: 88% of the cells were CD45, plus mononuclear cells with the following immunophenotype (Table 1):

Table 1. Results obtained from the sterna punction biopsy.

Myeloid markers	Lymphoid markers	Rest
CD13 18,3 %	CD2 neg.	CD34 38,8 %
CD33 99%	CD7 29,1%	HLA-OR neg.
CD14 neg.	CD19 neg.	CD117 44,3 %
CD15 neg.	CD79a neg.	CD79a neg.
MPO 14,3 %	CD10 neg.	CD79a neg.
TcT neg., CD22 neg.		

The test results were in favor of AML with aberrant expression of CD7. At the same time, the EBV test was again performed, and it was negative (0,77). The control blood analysis revealed values for WBC of 34,6 x 10^9/l.

Blood analysis was regularly performed in the following two days,. Leukocytosis was twice observed (30,94 x10 ^ 9 / L and 36,99 x10 ^ 3 mL). Five months after the onset of symptoms, a smear from a salivary gland was taken, with negative result. The comparative MRI revealed a reduction of the haematomas in both submandibular glands, which were almost completely resolved (there was a leftover of 1o mm). Both submandibular and parotid glands were enlarged, with homogenous appearance, edematous, with a restriction of the diffusion – a finding that indicates a persistent sialoadenitis. Focal pathological lesions were not observed, nor intraparenchymic, and locoregional pathologically changed lymph nodes. The major salivary glands' ducts were not dilated. There was a bilaterally present mastoiditis and otitis media with diffuse sinusitis, a finding that was not observed at the first examination. A blood test was again performed, and it alarmed about increased leycocitosys of 35.22 x10^3 mL.

In February 2017, a patohistological finding of the 2-cm bony part from iliac crest was obtained. The sections were stained with HE, Gimsa and immunohistochemistry for: CD20, CD3, CD10, CD235, Tdt, CD34, CD117, Myeloperoxidase, Neutrophil elastase, CD68, MAC 387 and CD15. Positive results were obtained for: CD235 (eritroid precursors 30-40%), CD34 (5-10%, with dispersed, interstitial arrangement), Myeloperoxidase (10%), CD68 (myeloid-histiocyte precursors 30-4%). The final conclusion from the patohistology and immunohistochemistry was that, taking into consideration the immaturity of part of the cell population, with no signs of maturation and negative expression for CD20, CD3, CD1 and TdT (positive CD34, myeloperoxidase, CD68 and CD235), and with ruled out lymphoid proliferation, as well as in accordance with the clinical picture, it was recommended to evaluate a possible AML. The analysis of mutation of genes NPM1, FLT3 and CEBPA (otherwise present in AML) showed negative results and no gene mutations were observed. The sternal punction aspirate was in favor of acute leukemia, with high infiltration with blasts of 60-70%. The patient was then hospitalized at the Clinic for hematology, from February 10, 2017 to March 03, 2017. Chemotherapy was administered by protocol and transfusion: Tr mass 34 doses, Er 4 doses. The control sternal aspiration biopsy showed around 15% blasts. The patient was again hospitalized from March 13, 2017 to April 06, 2017, when a treatment according to FLAG-IDA protocol was given.

After the treatment, the bilateral enlargement of the parotid glands was completely resolved and the disease entered into a phase of remission. Her older sister was found to be HLA-DNA identical, after which a bone marrow transplantation was performed, with uneventful post-transplantation follow-up.

Discussion

There are several conditions whose clinical picture is characterized by bilateral enlargement of the salivary glands. Often there are two or more causes which present with a similar clinical picture, which may be challenging for the physician, and it might lead in the wrong direction while setting the final diagnosis. In our case, we did a "step by step" process of diagnosis, by ruling out sialectasis, as well as bacterial, medicament-induced, immunological, congenital and tumor etiology of the bilateral enlargement of the salivary glands. What drew our attention the most, was the discontinuity of the results from serology analysis for EBV and the suspicion of possible lymphoproliferative malignant pathology. We received the first concrete result from the serologic analysis for EBV 3,5 months after the onset of symptoms, which was later confirmed twice, although always with different values, varying from "grey zone" to a positive result. However, the last serologic finding for EBV was negative. Infection with EBV usually occurs in early childhood, after which the virus remains to persist in a low number of B cells. EBV attacks B-lymphocytes, bonding to CD21 receptor and causing latent infection in vivo and in vitro[1]. There is a wide spectrum of LPD (lymphoproliferative diseases) which are related to EBV and which occur in patients with primary immunodeficiency, in patients with AIDS or with iatrogenic post-transplanatation immunosuppression, as well as in those who undergo other types of treatment, like methotrexate and tumor necrosis factor (TNF) alpha antagonists treatment. Recently it was proved that the presence of EBV might lead to the occurrence of EBV-positive LPDs in adult patients who do not show signs of immunodeficiency at all[2].

Co-infection with EBV may appear in Morbus Hodgkin, large cell lymphoma, and lymphoma in AIDS[3-6], but also in chronic lymphocytic leukemia in childhood[7]. Shlehofer et al.[8] documented an increased number of EBV-VCA (viral capsid antigen) in a study performed on 121 children with ALL in Germany, without PCR test. The patients with EBV have been shown to have a higher frequency of relapses of the disease and mortality, compared with those who have EBV-ALL. Infection with EBV in patients with acute leukemia is more frequent in B-cells ALL, compared to T-calls ALL. EBV-positive patients show a worse prognosis compared to others. However, the recent literature points out the controversy of the role of EBV in leukemia in childhood[9, 10]. In literature, the association between LPDs and EBV infection in adults is mostly seen. In our case, the patient was 26-year old, with no history of lymphoproliferative disease. Lymphadenopatia of the head and neck may be

the result of lymphoma[11]. Lymphomas of the salivary glands are very rare and mainly arise from B-cells[12]. The extranodal lymphomas are mostly Non-Hodgkin (NHL) and represent 10-20% of all lymphomas[13]. Non-Hodgkin lymphoma of a salivary gland usually presents as a painless mass that progresses quickly and increases in dimensions[14-17]. MALT lymphomas are most common among NHL of the major salivary glands. Low-grade MALT lymphoma of the parotid gland is usually a result of BLL (benign lymphoepithelial lesion)[18]. The transformation of BLL into MALT lymphoma is thought to be a "multistep" process. The initiation might be a long-lasting stimulation (activation) of B-calls by an inflammatory stimulus[19]. According to Rosenstiel et al.[20], in patients with Sjogren syndrome, the risk of non-Hodgkin is increased 44 times and 80% of those lymphomas are so-called MALT subtypes. According to Anacak et al.[21], MALT lymphomas of the salivary glands are more common in females. In their study the female:male ratio was 3:1. The cause of female predominance is unknown. In our case, all results from the examinations performed at the Clinic for rheumatology were negative (even when repeated). The bilateral enlargement of the salivary glands was limited (with no progression in dimensions since the initial examination), but they had become painful on palpation with time. Granulocytic sarcoma, or so-called myeloid sarcoma (MS) or "Chloroma" is a rare extramedular neoplasm, which consists of mature and immature granulocytes or monocytes. It is extremely rare to occur MS in patients with no previous history of myeloid neoplasm. It is present in 2,5%-9,1% of patients with AML and five times less in patients with chronic myelogenic leukemia. It occurs equally in males and females, and 60% of the patients are younger than 15. The number of cases with MS immediately after transplantation with allogenic stem cells is higher, and some authors suggest that MS is in fact a consequence of "graft versus leukemia" effect, that develops extramedullary[22]. MS also occurs in patients with AML and proven (8:21) cytogenic abnormality (translocation) i.e. in AML with maturation (M2) according to FAB classification. After the fine needle biopsy of four cases with MS of the salivary glands, the cytological evaluation showed spread acini of salivary gland, mixed with dispensed atypical cells. The atypical cells were heterogenous, medium and large in size, with wrinkled nucleolus with fine chromatin. In one case the cells showed homogeny, with rounded nucleoli and fine chromatin[23]. In our case, the fine needle aspiration biopsy showed hyperplasia of the ductal epithelium, with no cellular atypia.

Conclusion

The course of the diagnostics and treatment in the case reported in this study lead to a conclusion that there is no disease with whatever "benign" clinical presentation of longer enlargement of major salivary glands, which should not be underestimated. It should always be approached seriously and with no compromises. In our case, the initial impression of infective mononucleosis eventually led to a final diagnosis of AML. Bilateral enlargement of the major salivary glands is very rarely an initial symptom of AML, but the serious approach in line with interdisciplinarity allowed timely initiated and successfully performed treatment with long term remission of the disease.

Conflicts of interest

All authors confirm that there is no conflict of interest regarding this manuscript.

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