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Case Reports

SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY AND CONSTITUTIONAL APLASTIC ANEMIA

PLANOCELULARNI KARCINOM USNE DUPLJE I KONSTITUCIONALNA APLASTIČNA ANEMIJA

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Ključne reči
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Abstract

Constitutional Aplastic Anemia (CAA), also known as Fanconi´s anemia, is a rare autosomal recessive syndrome that is characterized by chromosomal aberrations and consequent congenital anomalies and progressive pancytopenia with progressive bone marrow failure. It is one of the syndromes with genomic instability that may predispose to the development of cancer. There is an increased frequency of leukemia, hepatocellular carcinoma and squamous cell carcinoma of the oral and anogenital regions in patients with CAA.
We present a new and rare case of oral cavity (buccal mucosa) squamous cell carcino¬ma of a 32-year-old patient with CAA.
Only 22 cases of CAA patients with squamous cell carcinomas of the oral ca¬vity have been reported in the literature. Up to our knowledge this is the the latest reported case of CAA with buccal mucosa squamous cell carcinoma, its diagnosis and treatment.

INTRODUCTION

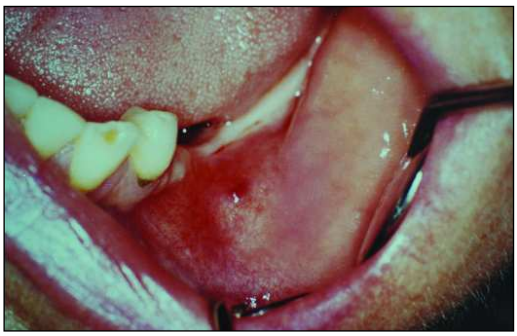
CAA is a rare autosomal recessive syndrome, affecting approximately one in 360,000 persons (1). It is characterized by progressive lethal pancytopenia, hypo-plastic bone marrow, several congenital anomalies and chromosomal aberrations. Somatic disturbances associated with CAA include growth failure, microcephaly, skeletal anomalies (absence or hypoplasia of radius and thumb), brown hyper-pigmentation of skin, predominantly in the flexures and on the lower trunk and neck, hypogenitalism and heart, kidney, ocular, auditory and central nervous systems abnormalities (1, 2, 3). The average age of onset of CAA is 4-7 years (4). Males are affected twice as often as females (4, 5). The typical patient dies of bone marrow complications or leukemia within the first two decades of life and most patients die within five years of becoming anemic (2), A less severe or incomplete form tends to develop malignancies more frequently than the severe form (2). Genetic studies have shown that affected patients have an increased number of chromosomal defects, which include breaks, gaps, fragments and dicentric centromeres (4). These changes can occur spontaneously but there is a greater susceptibility to viruses (5), X-rays, and cytotoxic drugs (4). In these patients there is a reduced capacity for DNA repair, particularly for the impaired DNA repair pathways (repair of DNA double strand breaks via homologous recombination) and monouboqutination. There are 15 genes in that pathway, some of them are also involved in replication, cell cycle control and mitosis. Patients with CAA are prone to develop hematological malignancies, hepatocellular carcinomas and squamous cell carcinomas, especially of the head and neck and anogenital región (2, 3, 6, 7). There are several reports of squamous cell carcinomas in patients with CAA. Most squamous cell carcinomas in CAA patients have occurred in the head and neck, particularly the oral cavity and the tongue.

CASE REPORT

The patient is a 32-years-old female with CAA diagnosed at age12. The patient has been treated since then with androgen therapy and intermittent blood transfusión. She presented typical signs of CAA, including small stature, hyperpigmentation of the skin and hypogonadism. A karyotype showed cytogenetic abnormalities. Bone marrow transplantation has not been performed because of lack of a suitable HLA-matched donor.

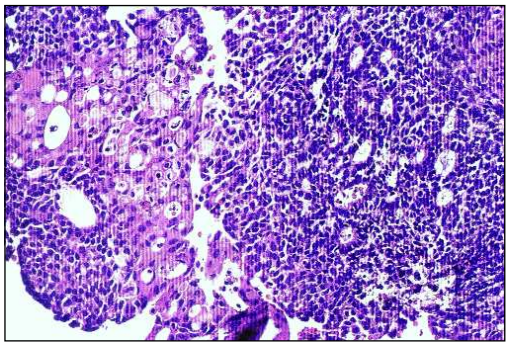
One year before presentation, the patient was admitted to our Hospital because she had developed an asymptomatic ulceration on the pretibial skin of her right leg. Skin examination showed a superficial ulcerative patch, 8x5 cm in size, containing necrotic tissue and bloody crusts. Two skin biopsy specimens were taken from the edge of the ulcer and submitted for routine histopathology and direct immunofluorescent microscopy studies. There were necrosis of the epidermis and a massive, predominately neutrophilic inflammatory infiltrate in the dermis. Direct immunofluorescence against Ig A, Ig G, Ig M, C3, and fibrinogen was negative. A culture from the lesión yielded Staphylococcus aureus. The diagnosis of pyoderma gangrenosum was made, and treatment with systemic prednisone (60 mg/day) was started. The ulcer disappeared in 5 weeks, leaving a hyperpigmented and atrophic scarring patch as residual lesión. There were no recurrences of the lesión in the following year.

The patient was referred to the Oral and Maxillofacial Service with a two months old buccal mucosa lesion. There was no history of smoking or alcohol consumption. The ulcerated lesion was located in the oral mucosa and measured 1,5x2 cm (Fig 1).



The ulcerated lesion was located in the oral mucosa and measured 1,5x2 cm ***(Fig 1)***

There was no cervical adenopathy and the rest of the head and neck examination was normal. An incisional biopsy revealed a well-differentiated squamous cell carcinoma (Fig 2).



Well-differentiated squamous cell carcinoma ***(Fig 2)***.

The laboratory findings included a hematocrit value 26.1%; hemoglobin value 8.2 g/dL; and white blood cells count of 1300/mm3 with a differential of polymorphonuclear neutrophilic leukocytes, 25%; lymphocytes, 68%; eosinophils, 2%; and monocytes, 5%. The platelet count was 26000/mm^3. She received 10 units of platelets the day before surgery and 10 additional units at the time of surgery. The patient underwent a wide local resection under general anesthesia with immediate re-construction with a local flap. Surgery was uneventful. Complete epithelisation of the buccal surface was apparent after 4 weeks. Microscopic examination showed that the surgical margins were free of disease and the diagnosis of well differentiated squamous cell carcinoma was confirmed. The patient is alive with no evidence of disease at nine months.

DISCUSSION

The propensity of CAA patients to develop secondary malignancies is well documented. The most common of these malignancies is acute leukemia. Other malignant lesions are solid tumors that have principally involved either the liver (hepatocellular carcinomas) or muco-cutaneous sites, especially in anogenital and oral sites (squamous cell carcinomas) [2, 5, 8]. The risk in non-transplanted patients with CAA of developing malignancy has been estimated to be up to 15,000-fold higher than that in the normal population [9]. Long-term survival obtained with bone marrow transplantation, the treatment of choice for CAA, may be associated with an increase of neoplasia in these patients [9]. A recent study suggests that by age 40, more than 50% of patients with FA will develope myelodysplastic syndrome or leukemia [9]. With regard to the incidence of solid tumors no firm figures are available [9].

Hepatocellular carcinoma has been reported in at least 12 patients. It has been suggested that the hepatic tumors may be induced by hepatocellular damage caused by the therapeutic administration of androgens [4].

Squamous cell carcinomas in CAA have a marked affinity for the mucous membranes of the anogenital and oral areas. Sites of involvement included the anus, vulva, cervix, skin, esophagus, pharynx, larynx and oral cavity. A review of published cases suggests that most are located in the head and neck region with the majority in the oral cavity [4]. The affinity of SCC to the oral cavity, and specially to the tongue, is especially striking. Florid focal epithelial hyperplasia of the oral mucosa has also been reported in patients with FA [10].

To date, squamous cell carcinoma in CAA has been reported in 56 patients. Twelve presented with anal, vulvar or cervix carcinoma [1]. Thirty two patients had head and neck squamous cell carcinoma and twelve were located in the oral cavity, with ten in the tongue [2, 3, 5, 11-16]. The gingiva is the second site of predilection of squamous cell carcinoma in the oral cavity in CAA [6, 14, 17]. Squamous cell carcinoma of the buccal mucosa in FA is extremely rare with only one case in the literature [18]. Synchronous carcinomas have been described by Kennedy [2], Guy [15] and Linares [7]. Kennedy reported a patient who sequentially had squamous-cell carcinoma ofthe vulva and tongue [2]. The patient

reported by Guy and Auslender was found to have primary hepatocellular carcinoma shortly after treatment for a lingual squamous cell carcinoma [15]. Linares reported a case of simultaneous hepatocellular and squamous cell carcinoma of the esophagus [7]. Multicentric oral squamous cell carcinomas have been reported in one case in which two separate oral squamous cell carcinomas developed in the tongue and gingiva [14].

Our patient developed a pyoderma gangrenosum one year before the squamous cell carcinoma of the oral cavity appeared. Pyoderma gangrenosum is an inflammatory non-infective ulceration of the skin which at about half of the cases occurs in association with systemic diseases such as inflammatory bowel disease, arthritis, paraproteinemia, hematologic malignancy and other conditions [19]. The mechanisms that connect the development of pyoderma gangrenosum may also herald the development of a solid neoplasia [19, 20]. This could be the case in our patient since CAA has not been previously described in association with pyoderma gangrenosum.

CAA is one of the chromosome instability syndromes that may predispose to the development of cancer and have been recognized as a group of inheritable genetic disorders. Included within this category of diseases are ataxia, telangiectasia, Bloom's syndrome, xeroderma pigmentosum, Cockayne's syndrome, congenital dyskeratosis and CAA [2, 5]. These diseases are characterized by an increased frequency of chromosome breaks and rearrangements or a defect in DNA repair [1, 4]. Except for Cockayne's syndrome there is a high incidence of malignancies in these disorders [1]. There are three postulated mechanisms that predispose CAA individuals to the development of neoplasia: defective DNA repair, defective detoxification of oxygen radicals, and immunodeficiency [5, 11].

The average age off CAA patients with oral cavity squamous-cell carcinomas at the time of diagnosis of their tumors, was 26 years. The patients' ages ranged from 11 to 44 years (our case 32 years). This contrasts with the average age of squamous cell carcinoma in the oral cavity in the general population (60-70 years). The development of squamous cell carcinoma of the oral cavity in patients younger than 30 is quite rare. It is likely that the risk for squamous-cell carcinoma to develop is greatest in those patients whose bone marrow problems are mild and are able to survive several decades.

The male/female ratio of patients with CAA is 2:1. This ratio is reversed among CAA patients who develop squamous cell carcinomas (2, 12). The female predominance suggests that hormonal factors may be involved in the pathogenesis of squamous cell carcinoma in CAA patients [2, 12].

Few patients died as a direct result of the squamous cell carcinoma. Most of them died from sepsis or complications associated with treatment of their malignancy. Mean survival was about 1 year after diagnosis of the squamous cell carcinoma.

The treatment for SCC occasionally includes surgery, radiotherapy and chemotherapy [12]. The main problem in CAA patients is the impairment of haematological and coagulation functions, so platelets and blood transfusions are usually to be given prior to surgery, as well as postoperative wide antibiotic coverage. In patients with CAA, because of the increased susceptibility of the tissues to the mutagenic effects of both radiotherapy and chemotherapy, these treatments have been considered potentially dangerous and are avoided. It has been suggested that routine X-rays may be hazardous [4]. Thus, surgery is the only useful therapeutically approach in the treatment of patients with squamous cell carcinoma and FA [4]. Periodical revisions of risk areas are strongly advised [4]

Sažetak

Konstitutivna aplastična anemija (KAA) poznata i kao Fankonijeva anemija je retko autozomno recesivno oboljenje, koje karakterišu hromozomske aberacije i kao posledica toga kongenitalne anomalije i. progresivna pancitopenija sa progresivnim slabljenjem funkcije koštane srži. Ovo je jedan od sindroma sa genomskom nestabilnošću i stoga predispozicijom za obolevanje od karcinoma. Kod bolesnika sa KAA povećana je učestalost oboljevanja od leukemija, hepatocelularnog karcinoma i planocelularnog karcinoma usne duplje i anogenitalne regije.

Prikazali smo redak slučaj 32-godišnjeg pacijenta sa planocelularnim karcinomom usne duplje (bukalne sluzokože) koji boluje od KAA.

Do sada su u literaturi prikazana samo 22 pacijenta sa KAA koji su oboleli od planocelularnog karcinoma usne duplje. Prema nama dostupnim informacijama ovo je poslednji opisan slučaj pacijenta sa KAA koji je oboleo od plnocelularnog karcinoma bukalne suzokože, sa opisom dijagnostike i lečenja.

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