Bilateral hand squamous-cells carcinoma in patient affected with non-Hodgkin lymphoma. Case report and literature review

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SUMMARY: Bilateral hand squamous-cells carcinoma in patient affected with non-hodgkin lymphoma. Case report and literature review.

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Background. Squamous-cell skin cancer is the most frequent tumor in the hand. It occurs on sun-damaged skin, especially in light-skinned individuals with a long history of chronic sun exposure.

Case report. We describe a case of bilateral hand squamous-cell carcinoma in a elderly patient affected with non-Hodgkin's lymphoma,

who underwent several non-successful surgical treatment, radiotherapy and at the least, amputation of right hand for rapid clinical evolution after radiotreatment. Available literature on the subject has been reviewed.

Results. In our case, after several non-successful treatment, elective amputation at the distal third of forearm was performed. We reviewed 56 items including books, original articles, reviews, cases report.

Conclusions. Current evidence on treatment of hand squamous-cells carcinoma is to perform a first radical surgical treatment in order to avoid recurrence/metastasis and to achieve a safer level of amputation thus increasing the surface area of healthy tissue available for eventually subsequent reconstruction/prosthesization.

KEY WORDS: Bilateral hand epithelioma - Amputation - Non-melanoma skin cancer - Squamous Cells Carcinoma (SCC) - Surgery.

Introduction

Non-melanoma skin cancer is the most common malignancy in the United States consisting of 80% basal cell and 20% squamous cells carcinoma (SCC) (1).

The occurrence of non-Hodgkin lymphoma and skin cancer are strongly associated (2, 3). Patients with non-Hodgkin's lymphoma have a overall 5.5% of relative risk for developing squamous cell skin cancer (3). Hand SCCs represent 10 to 15% of all skin spinocellular tumors (4) and are the most frequent malignant tumors on the hand (70 to 90%) (4-6). Bednail carcinoma is rare, often characterized by local malignancy, more common on thumb and second finger (7). The most common risk

factor for developing SCC is sun exposure to ultraviolet radiations (8). SCC is more common in skin areas with post-radiation dermatitis developed after the treatment of cutaneous conditions (9). It can present as papules or plaques, skin-colored or pink, smooth or hyperkeratotic. Over time, it can become a large, deeper, ulcerated or exophytic tumor. It is often itchy and easily bleeds when traumatized (10). The risk of metastases is high, particularly in immunocompromised populations (11, 12). It metastatizes by lymphatics or hematogenously (13).

Surgery is the main treatment for this kind of skin cancers: radical excision of the tumor with safe margins (14) or Mohs micrographic surgery (15). Confirmation of complete removal of lesion is required.

Because of low incidence of lymph node metastasis, ELND is not performed unless the axillary nodes are enlarged (13). Radiotherapy (RT) is therefore indicated for elderly patients not candidate for surgery. Adjuvant RT is required in large or recurrent tumors in multimodal treatment protocols (16-18). Adjuvant Systemic chemotherapy with 5FU is indicated only for large tumors and metastatic disease (19).

No standard treatment of metastatic disease has been formulated. Nevertheless combinations of cisplatin

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with 5-fluorouracil (5-FU), doxorubicin or bleomycin demonstrated some degree of efficacy, achieving complete responses in some cases (20).

We report a case of dorsal bilateral SCC of the hands with recurrence on the right hand and infiltration of palmar region, highlighting the clinical challenges in the context of the available literature.

Case report

We report a case of a 87 year-old man affected with non Hodgkin lymphoma, who was admitted to our service of Plastic Surgery of Policlinico Umberto I of Rome, in February 2013, presenting a skin lesion on the dorsum of his right hand (Fig. 1a), infiltrating the palmar region (Fig. 1b). The patient had been previously treated for two years in another hospital. On April 2011, he referred the emergence of a small dyskeratotic scaly spot on the dorsal surface of right hand. Lesion size gradually increased and was surgically excised on may 19, 2011. Histology documented a moderately differentiated squamous cells carcinoma that resulted incompletely excised in its deeper and lateral portion. After 2 months, the patient underwent a second surgery for local excision of the lesion. Histology of the skin lozenge and subcutaneous tissues (2 x 1 x 6 x 0,6 cm of a ulcerated and

depressed area of 1.2 cm) showed a moderately differentiated infiltrating squamous cell carcinoma (G2) ulcerated on the surface, incompletely excised at the sides and deeply (4.5 mm thickness). No signs of angioinvasion were documented (tumor in pT1). On October 2011, he underwent a third surgery, with lesion excision and skin graft closure. Histological examination of soft tissues (4.5 x 2.5 x 5 x 0.5 cm) documented keratinizing moderately differentiated spinal cancer cell (G2) of maximum diameter of 2.7 cm. The lesion was characterized by necrotic foci and abundant intratumoral inflammatory infiltrate of a mainly granulocyte type. Extensive areas of elastosis of the dermis and peripheral foci of carcinoma in situ were also reported. Surgical margins of resection appeared uninvolved (cancer in pT2 G2). On May 2012, the patient was admitted to the hospital for right hand ulceration and bleeding and small hyperkeratotic pink plaque on the dorsal surface of left hand. He performed bilateral radiotherapy of 300 cGy over 3 weeks, for a total tumor dose of 4500 Gy in 20 daily fractions from July, 30th to August, 20th for right hand and in 15 daily fractions from September, 28th to October, 19th for left hand. Apparently a bilateral complete tumor regression was obtained (Fig. 2 a, b) but just few months later, clinical conditions of the right hand (Fig. 1) changed with tumor recurrence. On February 2013, the patient was admitted to our Department for the first time. He was

Fig. 1 - Tumor lesion on dorsal surface of right hand (a) infiltrating the palmar region (b).

Fig. 2 - Left hand: current clinical pictures (a, b).

Fig. 3 - Imaging. a) Hand CT: almost complete osteolysis interesting the distal two thirds of the fourth metacarpal and the base of its proximal phalanx; osteolytic phenomena on the head of the metacarpal III and at the base of its proximal phalanx, too. b) Total body CT, abdominal particular: lymph nodes in the retrocrural, inter-aorto-caval and left para-aortic areas.

affected by chronic lymphocytic leukemia treated with dexamethasone 5 mg/day, with chronic portal vein thrombosis, hypertension and permanent pacemaker for atrial fibrillation (ASA III class for heart disease). At the physical examination, on the dorsal surface of the hand, he showed a large lesion with irregular margins and irregular shape, measuring 4.5 x 5 of maximum diameter deeply infiltrating the dermis up to the volar surface. The

center of the neoformation was ulcerated and bleeding, bumpy and with a hyperkeratotic periferic bead. The metacarpal and the proximal phalanx of the third finger were evidently involved. We performed radiological examination for staging before treatment. On January, radiography of the right hand showed widespread osteolysis interesting the distal two thirds of the fourth metacarpal and the base of its proximal phalanx. The head

of the metacarpal III and the base of its proximal phalanx were partially involved by osteolytic phenomena. Spiral CT (Fig. 3a) confirmed these data. Hints of degenerative joint disease, carpal bone sclerosis of the opposed articular surfaces and multiple small cystic areolas and osteopenia were also noticed. Ultrasound axillary lymph nodes bilaterally showed some hypoechoic formations with hyperechoic central nucleus as for preservation of vascular hilum whose maximum dimensions were about 17 mm to 14 mm with no specific meaning. No swelling of pathological significance nor clinical or ultrasonographic evidences were appreciated. Total body CT (Fig. 3b) showed several mediastinal prevascular, aorto-pulmonary, para-tracheal and subcarinal lymph nodes and abdominal lymph nodes in the retrocrural, inter-aorto-caval and left para-aortic areas. A space-occupying formation of 3 cm of diameter (lymph node formation due to the underlying disease chronic lymphocytic leukemia VS pancreatic neoplasm) was pointed out. We decided to surgically treat the patient. Elective amputations at the distal third of forearm was performed (Fig. 4).

Surgical procedure. After the positioning of Tourniquet, dorsal and volar antebrachial fascia were incised. Radial and ulnar vessels and nerves, median nerve and the anterior and posterior interosseous vessels were identified and ligated and tendons or muscle bellies divided and incised just distal to the desired level of bony resection. An incision in the periosteum was carried out circumferentially at the planned level with pair *Gigli* Saw Handles. The bone was transected at the planned level at this time and the specimen was removed. The bone ends were smoothed with a rasp. We performed hemostasis and wound closure using the skin flap after release of the Tourniquet: the subcutaneous tissue and skin were closed in separate layers. A drain was placed. The stump was circumferentially wrapped with an elastic bandage applied more firmly distally than proximally to prevent stump edema. Resected hand was sent for histology. Laboratory results documented a moderately differentiated squamous cells carcinoma with free resection margins.

Results

Elective amputation at the distal third of forearm guaranteed the oncologic radicality (Fig. 4). No recurrence was detected during the subsequent follow-up visits.

Discussion and conclusions

Some considerations must be made, being SCC the most frequent tumor of the hand (4-6, 21) and of the

Fig. 4 - Post-operative result after amputation at the distal third of the right forearm.

nail bed (7, 22). In fact, SCCs represent 10 to 15% of all skin spinocellular tumors and 70 to 90% of all malignant tumors on the hand (4). SCC is twice as common in men than in women (4, 23). Despite of their rising incidence, such tumors are only occasionally seen by the plastic surgeons because of their overall rarity (5).

They usually arise on dorsal surface of the hand, at metacarpal level (64%) or in commissures (31%) (6). Palmar localization is very rare (6, 24, 25). Rayner et al. (23) describe just 4 cases at the palm out of 273 analyzed cases. In our case SCC was localized at metacarpal level. The head of the metacarpal III infiltrated the palm of the right hand and the base of proximal phalanx were partially involved by osteolytic phenomena. Bednail carcinoma is rare, often characterized by local malignancy, more common on thumb and second finger (26). Authors (6, 27) underline the role of ultraviolet sun light, fair complexion, trauma (burn scars or osteomyelitis of long duration (23) and irradiation (9, 23, 28-30) as documented risk factors.

Glicenstein (6) stresses the role of precancerous tumors: solar keratoses, arsenical keratoses, radiation dermatitis, kerato-acanthomas, Bowen's disease and malignant tumors. In half of 422 lesions described, Maciburko

et al. (25) refer a history of previous skin cancer and one in five of patients developed multiple hand tumors. Radiodermatitis' risk for malign transformation is 10 to 55% (6). Lumpkin et al. (29)'s focus is on professional risk of doctors and paramedic personnel who use radionuclides and more in general in personnel administrating radiopharmaceuticals. Schiavon et al. (31) talk about "professional disease" in 15% cases out of 55 patients affected with hand SCC. In Haber et al.'s series (32), 38 out of 90 patients were dentists or physicians. Nelson et al. (9), Lejeune et al. (22), Foley et al. (30) and Capretti et al. (33) describe cases too (Table 1). Penn and Starzyl (34) report 3 cases of SCC of hand and forearm on 75 chronic survivors of organ transplantation and Walder et al. (35) refer 3 cases in patients underwent kidney allograft. Dandurand et al. (36) report a case of association between squamous cells carcinoma with chronic post-mastectomy lymphedema in skin areas with vitiligo. Gipsen (37) describes association with epidermolysis bullosa dystrophica. Association with Dupuytren's disease is reported by Haslik et al. (38).

As far as we know, few bilateral cases are described in literature. We found particular interesting association of third web space SCC with bilateral syndactyly described by Lam et al. (39) and Makoleba et al.'s report (40) of dorsum epithelioma in a patient affected with AIDS and bilateral hand burns. In our case, hand bilateral SCC was associated with chronic lymphocytic leukemia.

Tropet et al. (4) and Lumpkin et al. (29) relate the difficulty in the differential diagnosis because there are several clinical forms of similar appearance but of benign nature. In particular, Tropet (4) underlines that the tricky differential diagnosis with ketatoacantoma, is based on architectural criteria rather than cytological. All authors (4, 17, 20, 25, 28) recommend early diagnosis and pathologic analysis. Early detection, in fact, decreases the morbidity associated with the locally destructive nature of these tumors (17).

Appropriate treatment consists of surgical excision of the tumor with a margin of safe tissue or amputation. Lymph node dissection is recommended for clinically positive nodes in special circumstances, and careful follow-up for recurrence or metastasis is mandatory (4, 17, 20, 23, 25, 28).

Preoperative and intraoperative pathological biopsies are indispensable, in consideration of the degree of malignancy and the possibilities of surgical reconstruction (28). Non surgical treatments are indicated for elderly patients not candidated for surgery, as well as adjuvant in large or recurrent tumors requiring multimodal treatment protocols (13-15). Bean et al. (28) report non-surgical treatment with cryosurgery, curettage, 5-fluorouracil, or irradiation. We do not recommend cryosurgery or curettage because it is impossible to perform

histological analysis and then to assess the accuracy of the intervention, the course and the prognosis.

Tropet et al. (4) and Rayner et al. (23) indicate that squamous carcinoma of the hand behaves more aggressively and is more difficult to treat by non-surgical means, when it arises in the interdigital clefts or adjacent skin over the metacarpo-phalangeal joints, where lesions are often aggressive or complicated. In fact, metacarpal space does not allow wide excision of soft parts which are the most susceptible. Rayner et al. designate the area corresponding to proximal phalanges, clefts and thumb as the "danger area". Outside this area, radiotherapy is as safe as surgery (96% cure rate) but surgery is quick (23). Maciburko et al. (25) confirm these observation even if in their series of 422 hand SCC cases, the recurrence rate in the danger zone was similar to the other areas of the hand. In our case, SCC was localized at metacarpal level and the head of the metacarpal III and the base of its proximal phalanx were partially involved by osteolytic phenomena. Even palmar localization tumors are difficult to treat and they might rapidly diffuse (41).

Authors stress the importance of achieving free resection margins, in order to decrease the risk of recurrence. Recommended excision margins for skin squamous cells carcinoma vary from 2 to 15 mm, according to Thomas et al. (42). In hand tumors, Joyner et al. (21) recommend wide excisions with 1 to 2 cm margins and Glicenstein (6) 5 to 10 mm. It is useless to overcome the cutaneous plane unless there is clinical invasion but amputation is required if the lesion adheres to the perimysium (6). According to Schiavon et al. (31), for primary lesions over 2,5 cm of diameter or invading deeper layers, removal of the entire anatomical structure is advised (i.e. fascia, tendons, muscles, bone, entire rays or the hand itself). For lesions under 2,5 cm removal of a wide border is recommended. In this regard, our patient underwent several incomplete surgical treatments before coming to our department and even after radiotherapy the lesion showed a rapid progression and local tissue destruction. We performed elective amputations at the distal third of forearm. Proximal amputations can be devastating for the patient, with serious physical, psychological, social, and economic consequences. Nowadays prosthetic advances have helped many patients lead a better life and, often, return to activities they were involved in before their amputation. and to be initially aggressive in the eradication of the tumor, may lead to a safer level of amputation thus offering surfaces of healthy tissue available for subsequent optimal reconstruction and prosthesis. Untreated lesions are locally destructive and may cause functional deficits and death by way of metastasis, as stated by Fink et al. (5). Regional lymphadenectomy is required for clinically positive nodes or in special circumstances (4, 5, 17, 20, 23, 28).

TABLE 1 - ASSESSED CASES. (continue)

Authors	Cases	Age	Sex	Site	Side	Precancerosis/ Associated clinical conditions	Lymph nodes	Treatment	Adjunctive treatment	Recurrence	Metastases
De Bell and Stevenson ⁴⁸ (1936)	44	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Surgery	Unknown	11%	14%
Sigel ⁴⁹ (1937)	1	70	M	Forth finger	L	Unknown	Unknown	Excision	Mould Radiotherapy	Unknown	Unknown
Taylor ⁵⁰ (1940)	284	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Surgery	-	Unknown	7%
Johnson and Akerman ⁴⁶ (1950)	72	Unknown	Unknown	Hand Forearm	Unknown	Unknown	Unknown	Surgery Radiotherapy	-	0%	Axilla 14% Epitrochlea 1,4%
Lawrence ⁵¹ (1953)	58	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Surgery	-	Unknown	25%
Kendall ⁵² (1969)	56	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Surgery Radiotherapy	Radiotherapy	Unknown	8%
Gipson ³⁷ (1975)	1	38	M	Hand	L (1967) R (1973)	Epidermolysis Bullosa Dystrophica	Unspecified	Amputation through the midhumerus Amputation through the wrist joint	- -	Elbow -	Right hand. Second tumor or metastasis? -
Forsythe ⁴³ (1978)	41	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Surgery	Radiotherapy	Unknown	11%
Rayner ²³ (1981)	273	>40, >60 (80%)	M:F 4:1	Palm 2,6% Dorsum 97,4%	Unknown	6% of cases	Unspecified number	Elective surgery: 9% - Excision and graft: 16 pt - Amputation: 8 pt "Unplanned surgery": 24 pt	Amputation after radiotherapy: 14 pt	20% of cases treated with a radioactive mould; 52% of cases treated with external beam irradiation; 13% of cases	10%

TABLE 1 - ASSESSED CASES. (continue)

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TABLE 1 - ASSESSED CASES. (continue)

									Lymphadenectomy Radiocarpal disarticulation Above-elbow amputation				
Lejeune ²² (1989)	3	58	M*	II finger	R	Radioderm atitis I, II, III finger	-	Elbow	II finger amputation Chase type at metacarpal- phalangeal level + palmar biopsy first and second finger Tumor excision + elbow lymph nodes dissection Thumb distal phalanx amputation	-	-	-	Elbow
		49	M	Thenar eminence	R	-	-	Elbow	Radiother apy on thenar eminence and elbow	-	-	-	Elbow
		49	M	Subpara nails radial part thumb	R	-	-	-	-	-	-	-	-
Nelson ⁶ (1990)	1	75	F*	Flexor surface middle finger	R	Radiodermatitis	-	-	Right middle finger amputation	Unknown	-	-	Unknown
Bramhall ⁴⁷ (1991)	1	80	M	Dorsum	L	-	-	Axillary	Excision and skin graft	-	-	-	Forearm skeletal muscle
Foley ³⁰ (1995)	1	52	M***	Terminal pulp ring finger	L	Radiodermatitis	-	Axillary	Amputation of the distal phalanx of the ring finger, debulking of the axillary lymphadenopathy	Extremal beam Radiotherapy axilla and supraclavicular fossa + Bleomycin and Cisplatin	- (6 years observation)	-	-
Capretti ³³ (2004)	1	44	F****	Base of III finger	R	-	-	-	Removal 1 cm from the lesion	-	-	-	-
Ağır ²⁴ (2007)	1	74	M	Distal part of the palm	R	-	-	EpirocLEAR and axillary (after recurrence)	Excision ray Amputation involving index and middle fingers	Radiotherapy	Dorsum of the hand	-	EpirocLEAR and axillary lymph nodes, fatty subcutaneous tissue.

TABLE 1 - ASSESSED CASES.

												Cutaneous and subcutaneous metastases, in the thoracic wall and wides pread lung metastases
Joyner ²¹	32	Unknown	Unknown	Unknown	Unknown	Unknown	Marginal surgical excision 3 cases of reintervention for positive margins	Unknown	Unknown		Unknown	1
Lam ³⁹ (2009)	1	81	M	Third web space	L	Bilateral Third hand web space syndactyly	Ray amputation and local flap reconstruction to the middle finger Excision an split Thickness skin graft	-	-		-	-
Haslik ³⁸ (2011)	1	49	Unknown	Unknown	Unknown	Dupuytren's disease	Resection	Radiotherapy	-		-	-
Makobela ⁴⁰ (2012)	1	31	M	Dorsum	R, L	Bilateral hand burns AIDS	Excision and free flap	-	Unknown		Unknown	Unknown
Maciburko ²⁵ (2012)	422	72 (mean)	M:F 1,9:2	Dorsum 50%	R 51%	Previous skin cancer: 22% Renal transplant: 16,5%	Excision: 85,8% Amputation: 3,6%	Lymphadenecto my: 2,9%	2,9%	2.1%		0%

Notes

*Radiologist, Radiotherapist and Nuclear Medicine Doctor

** X-ray Technologist

*** Dentist with professional radiodermatitis

**** Nurse who worked for 3 years in a Metabolic Radiotherapy Unit

a. Palliative surgery: operation was not a formal attempt at cure.

Bean et al. (28) Forsythe et al. (43) and Tomsick et al. (44) recommend lymph nodes dissection just for palpable lymph nodes. Forsythe et al. (43) suggest lymphadenectomy only if lesion is located within a worse prognosis area as commissures, mobile areas or palm. Schiavon et al. (31) refer 22% recurrence rate over 55 patients and in 67% of cases recurrence was associated with metastatic spread. Systematic lymphadenectomy is suggested in cases of recurrence for increased risk of metastatic spread and even if lymph nodes may not be palpable. In literature no encouraging results from prophylactic lymphadenectomy are reported (45, 46). In presence of metastatic lesions, lymphadenectomy seems to give a good chance of survival: of the patient with regional lymph node metastases who had lymph nodes dissection, 54% were alive at 5 years after operation (31).

Radiotherapy is reserved for patients that cannot be operated or as a supplement or palliative, at the level of the hand or any metastatic focus. Bean et al. (28) and Tropet et al. (4) observe that recurrence rate is lower in patients who received a surgical treatment (3%) than in those non surgically treated (33%). Bean et al. (28) report 13% of recurrence rate in patients treated with surgery and 17% in those with nonsurgical treatment instead Rayner et al. (23) refers respectively 13% and 52%. According to Bean et al. (28), recurrence is greater (9%) and metastasis more common (38%) in patients with Marjolin's type of secondary squamous cell carcinoma than with solar-induced lesions. Fink et al. (5) refer 7 to 22% of recurrence rate after simple excision. Bramhall et al. (47) refer that metastases are infrequent. Tomsick et al. (44) remark that their frequency depends on some factors: former state of the skin, dimensions (macroscopic diameter greater than 20

mm25) spread in depth (tumor thickness greater than 4 mm25), involvement of subcutaneous fat and tendons or bone and the degree of cell differentiation. In Schiavon et al.'s (31) series, lymphatic metastasis appear 35 months after surgery.

Mortality rate data can vary. Forsythe et al. (43) refers 13% at years 3, Rayner et al. (23), 6 at years 5 and Schiavon et al. (31) 5 and 8 years mortality of 10% and 17,5% respectively.

Cutaneous lesions of the upper extremities should not be underestimated although they are very rare. In fact, functional importance of the hand in daily relation life requires particular attention in the choice of the best treatment. It is imperative to choose a first step radical treatment in order to avoid recurrence and metastases. In this regard, to be initially aggressive in the eradication of the tumor, may lead to a safer level of amputation thus increasing the surface area of healthy tissue available for eventually subsequent reconstruction and prothesization (48-55). Moreover it potentially decreases patient's number of treatments, hospital stay and last but not least, could reduce sanitary burden related to complex medical dressings and hospital care.

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