Cancers of the anus and the perineum - acute manifestations and short note of treatment

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Abstract

Tumours of the ano-perineal region are infrequent, and often difficult to identify based on their symptoms, especially if these are acute. Objective of this paper is to review the medical literature on ano-perineal tumours with specific attention to their acute symptoms at presentation.

Method: A medline search was carried out including every article published since 1980 that refers to tumours of the anus and the perineum presenting with acute symptoms.

Results: Tumors of the ano-perineal region, when presenting with acute symptoms often simulate more frequent benign inflammatory disease such as anal fistula or abscess. This leads to frequent misdiagnosis and delay in treatment.

Conclusion: Because of their infrequent occurrence tumours of the ano-perineal region are difficult to diagnose, especially when presenting with acute symptoms. A high index of suspicion and liberal use of biopsy and Nuclear Magnetic Resonance (NMR) imaging may lead to earlier diagnosis and improvement in the prognosis.

Keywords: perineal cancer, anal cancer.
Tumours of the anus and of the perineum have variable clinical presentation: acute sepsis is one of the most common, with symptoms such as painful mass, fever and fistulization.

The variety and rarity of ano-perineal neoplasms makes gathering and organizing scientific information difficult. Although Medical literature is abundant in case reports, it offered little help in uniformly approaching acute presentation of ano-perineal tumours. Moreover the rarity of these tumours makes the formulation of a unanimously accepted treatment more difficult. Aim of this study is to evaluate the acute symptoms at presentation of ano-perineal cancers.

Method: All medical articles from 1980 in which were present the key words “acute” or “emergency” and “anal cancer” or “perineal cancer” or “perianal cancer” were reviewed. All related articles were also evaluated.

Results: After a review of the selected publications the information was organized according to the histologic tumour type.

**Epidermoid carcinomas** rarely appear with urgent symptoms: in fact, even at an advanced stage the symptoms are not distinct from chronic benign disorders such as haemorrhoids and fissures; sepsis is usually due to neglected disease. However, some cases presenting with abscesses and fistulas have been described. Carcinomas of the anal canal account for 1-2% of colorectal tumours and for 2-12% of anorectal neoplasia. Eighty-five % of anal cancers are epidermoid tumours and account for 3% of gastrointestinal carcinomas. Tumours of the anal canal affect more frequently older females (M/F 1:3), mainly black single females who live in metropolitan areas and are smokers. Females who have a Human Papilloma Virus (HPV) infection carry a greater risk (3 times more) of anal cancer. The percentage of cancer of the anus among HIV+ patients is relatively high particularly among homosexuals and it is twice in comparison to homosexuals who are not HIV+. HPV infections in the anal canal lead to the formation of flat condylomata that are difficult to visualize but may become evident under high resolution anoscopy after the application of a 3% solution of acetic acid or of Lugol solution. The most significative risk factor for the development of invasive anal cancer in HIV+ patients is the length of disease. As a result of the increase of survival, thanks to new retroviral therapies, cancer of the anus has become an increasing problem. Anti-HPV16 (peptideE2 and E7) antibodies have been found in 55% of patients affected by epidermoid anal carcinoma. Recent studies have identified genetic factors such as frequent deletions at chromosomes 3p, 6 and 10p and epigenetic alterations such as inactivation of the TLSC1. The HPV related transformation of the epithelium is a multi-step process, which involves a deregulated transcription of viral oncoproteins E6 and E7. The interference of E6 and E7 with the regulators of the cell cycle leads to chromosomal instability. HPV carcinogenesis seems to differ in HIV+ patients since microsatellite rather than chromosomal instability is observed. With the introduction of a highly active retroviral therapy there has been a decrease of HPV related cancer in HIV+ patients. Trans-anal ultrasonography accurately defines local extension of the disease, invasion of sphincter and adjacent organs and the state of mesorectal lymph nodes. Ultrasound T staging was shown to be the only independent factor predicting survival in a multivariate analysis. Synchronous metastasis to groin lymph nodes occur in 10-25% of patients and metachronous metastasis in 5-25% of patients. In a multivariate analysis groin lymph nodes metastasis are among independent prognostic factors for both local recurrence and mortality. The technique of sentinel lymph node (SLN) biopsy is an easy and secure method of evaluating the lymph node status and for obtaining an adequate staging before treatment. In fact negative results make radiotherapy to the groins unnecessary while positive results indicate complete radiation therapy with an extension to the iliac nodes. For SLN biopsy, patients undergo a lymphoscintigraphy after a peritumoural injection of colloidal TC-99. In a review evaluating the efficacy of the procedure 5 studies were analyzed including 84 patients: the SLN was found in 66% to 100% of cases. Of these between 7% and 42% were metastastic. Moreover patients with negative sentinel lymph node did not have groin relapses at a mean follow up time of 18 months. Prophylactic irradiation of the groin is therefore indicated in pN1SN and may not be indicated in pN0SN therefore avoiding treatment related morbidity. The side of groin metastasis is correlated with tumour location. Tumours located on the midline of the anal canal are associated with bilateral lymph nodes in 89% of cases. When the tumour is located on one side of the anal canal synchronous or metachronous metastasis of the groin is ipsilateral in 100% patients. The main treatment of anal cancer is chemotherapy combined with radiotherapy.
Failure to respond to this treatment is a poor prognostic sign. For in situ tumours (< 10 mm) treatment can be local excision only without radiotherapy. For T1 stage tumours local excision is preceded only by external radiotherapy at a medium dose of 45 Gy boosted by brachitherapy with a dose of 20 Gy. Combined modality treatment with radio and chemotherapy allows good functional results and local control of the disease. Standard chemotherapy is 5FU in combination with mitomycin (MMC) but cisplatin (CDDP) is an efficient substitute and is better tolerated than mitomycin. Favourable results have been obtained in terms of toxicity and of local control in phases II/III studies in and in retrospective studies. More recently capecitabine, an oral form of 5FU has been used. Survival after chemotherapy with CDDP seems to be equal or superior to the results of surgery in patients with residual disease at six months from initial non-surgical treatment. In HIV+ patients standard chemotherapeutic regime must be reduced because such individuals develop major toxicity especially when CD4 count is inferior to 200 and therefore require longer intervals between treatment cycles. Conformational radiation therapy reduces the width of the field and therefore the dose to the unaffected small pelvis, bladder and genitals compared to the affected areas. This combines a reduction of acute toxicity with optimal local control of the disease. Standard chemotherapy is 5FU in combination with mitomycin (MMC) but cisplatin (CDDP) is an efficient substitute and is better tolerated than mitomycin. Favourable results have been obtained in terms of toxicity and of local control in phases II/III studies in and in retrospective studies. More recently capecitabine, an oral form of 5FU has been used. Survival after chemotherapy with CDDP seems to be equal or superior to the results of surgery in patients with residual disease at six months from initial non-surgical treatment. In HIV+ patients standard chemotherapeutic regime must be reduced because such individuals develop major toxicity especially when CD4 count is inferior to 200 and therefore require longer intervals between treatment cycles. Conformational radiation therapy reduces the width of the field and therefore the dose to the unaffected small pelvis, bladder and genitals compared to the affected areas. This combines a reduction of acute toxicity with optimal local control of the illness. For local regional relapses, the preferred treatment is abdomino-perineal resection (APR). Radiotherapy prior to salvage surgery increases wound complications. In an article analyzing perineal wound healing after salvage APR, 11 of 18 patients had primary closure of the perineal wound, in 3 patients the wound was left open and in 4 patients it was closed with rectus abdominis myo-cutaneous flap. All dehiscences occurred in patients treated without flap reconstruction. Vaccinations are based on the induction of an immunologic response against infected cells expressing viral antigens E6 and E7 resulting in humoral immunity against viral capsid proteins L1 and L2. The results are encouraging.

**Perianal Bowen's disease** is another rare disease. It is an intraepithelial non-keratinizing carcinoma, that has been historically associated with anal or cervical epidermoid cancer. The increased rate of HPV-related cancer suggests a causative role. Chronic arsenism is advocated as a possible cause of Bowen's disease. The risk of other abdominal malignancy is not higher than in the general population. Bowen disease often appears with pain (4%) and bleeding (24%), and also with signs of mass and itching. Surgical excision is considered the preferred form of treatment, but there are controversies on the extent of the surgical margin: in fact local recurrences are in the non-excised perianal skin. If the margins of surgical excision are tumour free, local relapse is unlikely. Wide resections may require the use of reconstructive flap. In case of large lesions a 16 weeks course of 5% topical 5-FU has been successfully used in a study with 6 years follow up. In a recent retrospective study including tumours outside of the perianal region, Bowen's was treated with radiation therapy. Schedules were not uniform in doses and fractions, nevertheless the results were encouraging with a local control rate of 93%. Photodynamic therapy has been successfully used for residual disease but due to the low number of treated patients this technique remains experimental. The same applies to the use of Argon laser and pulsed dye laser both published in case reports. Local treatment with imiquimod has been used with success.

Cases of **adenocarcinoma of the anal canal** that develops in a longstanding anal fistula are rare and may present as acute local sepsis. Mucinous carcinoma with infiltration of the perineal skin has also been described in Paget's disease. By some authors it is considered a rare variant of anal canal epithelioid tumours. Mucinous adenocarcinoma has been found in rectovaginal fistulas associated with long history of Crohn's disease and has been described as a rare complication of Crohn's disease after proctocolectomy. Also cancer of the rectum may rarely present with a perineal abscess or fistula. The rectal origin can be ruled out with a histochemical test for sialic acid, as no trace of sialic acids can be demonstrated in the anal glands. The most common acute symptoms are anal pain, rectal bleeding, discharge and perianal mass. Symptoms are similar to those of benign anal inflammatory conditions, a fact that often contributes to delayed diagnosis. Anal glands carcinoma accounts for less than 10% of all carcinomas developing in the anal canal. It seems to be more frequent in males with a long history of perianal disease, and in the mid-fifty age group. It has been a matter of debate whether the adenocarcinoma origins from the rectal mucosa or from the anal glands, but the basis for a correct diagnosis is the histochemical examination that points out the absence of sialic acids which excludes the origin of cancer from the rectum. When
sialic acid is present it is believed that this tumour could have originated from the rectal mucosa, and from there migrated into the anal fistula. Metastasis at presentation are present in 13% to 62% of patients. The most common sites of metastasis are regional lymph nodes, liver, lung, and peritoneum. Surgical resection is the first choice of curative treatment, and additional treatments include chemotherapy, radiotherapy and brachytherapy. Favourable outcome was reported after treatment with external radiotherapy followed by high dose brachytherapy. The reported 5-year survival rate ranges between 5% and 40%. The rarity and apparent heterogeneity of this tumour does not allow any comparative study on the treatment. Up to the present day we don’t know whether it is possible to differentiate treatment and natural history of anal squamous or cloacogenic tumours based on histology and anatomic location. Such forms have also been described with a Pagetoid infiltration of the perineal skin.

**Anal melanoma** has been described in literature in little more than 300 cases. The first and most frequent symptom is anal bleeding. The decision whether to carry out local excision with histological free margins or whether, as the majority of authors advocate, to resort to an APR remains controversial. Neoadjuvant radiotherapy followed by local excision has been proposed. Nevertheless, as reported in one of the largest published series, anal melanoma has a poor prognosis because of the frequent systemic dissemination: eleven of the 12 patients died with metastasis and only 6/14 patients survived 1 year after treatment. Local excision is followed by high rate local relapse (60%) requiring further surgery. In conclusion, as reported in a review, melanoma continues to be associated with a poor prognosis.

**Merkel’s tumour** is a neuroendocrine carcinoma typical of the skin exposed to sunrays. In a case report it was mistaken for a post-partum bleeding haemorrhoid. Excision allowed a correct diagnosis of the disease when it was already metastatic. Local excision is the only course of treatment for this disease, which is usually lethal.

**Buschke-Lowenstein tumour** in its perineal variant is a rare disease secondary to HPV infection. Its pathological characteristics are benign, although it infiltrates and destroys the surrounding tissues. Advanced neglected disease may require urgent treatment for erosions into the rectum and the vagina. At this stage, it is difficult to carry out local excision of the tumour.

**Lymphomas** of the anal and perineal region are infrequent. Leukaemia of the anoderm, is quite rare. It may appear as perineal ulceration with cutaneous infiltration, but at times, erythema, fistulas or abscesses are absent. Nevertheless, a large perianal mass has been reported as its first sign. The diagnosis is obtained only after the histological exam on biopsies and with appropriate blood tests; it is important to stress that treatment should be conservative (sitz baths, antibiotics, and radiotherapy) and surgery is indicated only when there is a high risk of fulminant sepsis. *Burkitt’s lymphoma* is a disease affecting young people and is endemic in tropical Africa. It is frequently localized to the face and the abdomen, but rarely may occur in the perineum. It may appear as a perineal abscess, and only the pathologist is able to offer a correct diagnosis based on biopsies. *Angiocentric T-Cell lymphoma* is a typical subcutaneous lymphoma which is mistaken for panniculitis and rarely appears as a lesion of the perineum. The differential diagnosis, once again, is made from the more frequent perianal abscess. In a case report the isolation of a *Staphylococcus Aureus* delayed the diagnosis of neoplasia which was established only after weeks with histological exam of the abscess wall.

**Paget’s extra-mammary disease** is rare and may appear in the external genital region, followed by the perineum and the axilla. Cases of triple perineal, genital and axillary localization have also been described. In these cases a higher expression of the CK7 gene is found. The initial symptoms are erythema, pigmentation and cutaneous erosion. When the neoplasia infiltrates the deep tissues, it may require surgery because of severe secretion and pain. Unfortunately there is no specific treatment of the acute symptoms; the treatment of the neoplasia itself is not always well defined; treatment of first choice is extensive surgical excision, but local recurrences are frequent. When the area affected is wide and circumferential, staged excision, and coverage with full thickness skin graft, is considered easier to carry out than transpelvic myo-cutaneous flaps, in order to avoid a diverting colostomy. However this approach is followed by a considerable recurrence rate. The role of chemoradiotherapy remains undefined in this disease and the benefit of radiotherapy is controversial. Neoadjuvant or adjuvant chemoradiotherapy have both been suggested.
Rhabdomyosarcoma of the perineum may affect organs and soft tissues of the pelvis mainly in young children and adolescents. In the majority of cases, this tumour presents as a perineal mass mimicking an abscess, to the extent that in all the 11 cases presented, initial treatment consisted in antibiotics and incision with drainage before cancer was suspected, diagnosed with biopsy and staged with nuclear magnetic resonance. In adults it is a rare occurrence and requires local aggressive surgical treatment; it was suggested that more extensive and radical first intervention leads to a decrease of the disease recurrence. In contrast, in two young patients a conservative approach with local excision and neoadjuvant or adjuvant chemo-radiotherapy, has been described with preservation of anal function and a long term tumour free survival. In the sarcoma group the gastrointestinal stroma tumour (GIST) of the anus belongs to the group of very rare tumours. It presents with rectal haemorrhage and ano -rectal palpable mass. In a case report, transanal excision and long term survival have been described.

Kaposi's sarcoma is highly frequent in people with AIDS diagnosis, but the anal area is affected very rarely. From an epidemiologic point of view, it has been found that for patients treated with highly active antiretroviral therapy, the AIDS-defining cancers - as Kaposi's sarcoma and non-Hodgkin's lymphoma - may be balanced by the increasing numbers of non AIDS-defining cancers. Unlike anal HIV-associated cancers, the introduction of highly active antiretroviral therapy (HAART) has improved the incidence, clinical features, or overall survival. In addition HAART alone has been successfully used as therapy for early Kaposi's Sarcoma.

Perineal necrotizing cellulites has been described in association with ulcerated and suppurated rectal cancer. The infection involves pelvic-perineal layers like in Fournier's syndrome with oedema, fever and perineal pain irradiating to the genitals. The germ more frequently involved is "Pseudomonas aeruginosa". Treatment is carried out urgently, and consists in antibiotic therapy (broad spectrum), surgical debridment and diverting colostomy. Hyperbaric oxygen therapy may help decreasing tissue loss and promote wound healing. Surgical treatment of cancer of the rectum can be carried out simultaneously or at a later stage, once the conditions of the patient have become stable.

As we have seen, some of the ano-perineal cancers may appear as an abscess or a mass with a fistula, with more or less rapid growth. It is noteworthy that the same cases may be due to benign neoplasias, which may be locally invasive, such as a pseudotumor caused by ray-fungus disease, leiomyoma, haemangioma, and angiomyxoma. The last two forms will be discussed because of their particular aggressiveness.

Hemangiomas may present with perineal ulcerations. Although the pathology is benign, early diagnosis is preferable in order not to miss a more aggressive malignancy.

Aggressive angiomixoma is a mesenchymal tumour that develops from the connective tissue of the perineum or from the pelvis. It is a tumour of great dimensions, and appears as a mass in expansion and/or pain. After an accurate topographic definition with nuclear magnetic resonance (NMR), the surgical procedure chosen is the double access through the abdomen and the perineum. Radical removal of the mass may be difficult due to the widespread sclerosis that involves the pelvic organs.

Between tumour metastasizing to or directly invading the anus or perineum, the Erysipeloid carcino, from cutaneous metastasis of bladder cancer as well as perineal metastasis of testicular choriocarcinoma, may present as a hard and ulcerated nodule and mistaken for perianal infection. The nodules appeared reddish and painful and only a histological exam is able to offer a precise diagnosis.

In all neoplastic diseases presented, the best examination to undergo once tissue is obtained for histological exam is NMR, which provides information on size and boundaries of the mass, anatomy of the fistulous tract, presence of deep abscesses, as well as possible infiltration of rectal wall and the perirectal spaces.

In conclusion, every acute anal and perineal manifestation that leads to surgical intervention, must be carefully evaluated. The rare diseases described must be part of the differential diagnosis and excluded, because delayed diagnosis and inadequate treatment may be devastating for the patient, with possible legal controversies.
References


23. Ortholan C, Francois E, Gerard JP, Chemoradiotherapy and anal canal


45. Graham BD, Jetmore AB, Foote JE, Arnold LK. Topical 5-fluorouracil in the management of extensive anal Bowen's disease: a preferred approach. .....


68. Tan YS, Nambari R, Sim CS. Adenocarcinoma associated with chronic


