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Direttore Nicola Picardi

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Antonio Giuliani*, Federica Romanzi**, Alessandra Di Sibio***, Giuseppe Calvisi °, Loreto Lombardi°°, Michele Marchese°°, Mario Di Staso °°°, Mario Schietroma*, Francesco Carlei*, Lucia Romano*

**Department of General Surgery. Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy*
***Department of Obstetrics and Gynecology, University of L'Aquila, L'Aquila, Italy*
****Department of Radiology, University of L'Aquila, L'Aquila, Italy*
°U.O.C. Anatomia Patologica, ASL1 Abruzzo, "San Salvatore" Hospital, L'Aquila, Italy
°°Surgical Endoscopy Unit, San Salvatore Hospital, L'Aquila, Italy
°°°Radiotherapy, San Salvatore Hospital, L'Aquila, Italy

Hypovolemic shock after pelvic radiotherapy. A rare combination leading to a devastating complication

BACKGROUND: *Radiotherapy currently plays a key role in pelvic malignancies' management. Excellent outcomes have been reported on its association with chemotherapy for the treatment of the anal carcinoma. Despite that, the combined use of chemo- and radiotherapy and the high doses administered seem to be strongly associated with early and late onset side effects.*
METHODS: *We reported a case of a 72 years old woman, affected by anal squamous cell carcinoma. She underwent chemotherapy, and then radiotherapy, with good results.*
RESULTS: *During a regular MR control, the patient developed anaphylactic reaction to Gadolinium, and after that a rectosigmoid ischemia with total necrosis of the posterior rectal wall was diagnosed and surgically treated with Hartmann procedure.*
CONCLUSION: *In our case we faced with the rapid and severe degeneration of pelvic anatomy determined by the sum of vascular alterations following hypovolemic shock and pelvic tissues alteration after radiotherapy. It seems essential not to underestimate the exponential outcome of a similar unusual combination of events.*

KEY WORDS: Anal carcinoma, Hypovolemic shock, Pelvic radiotherapy, Rectal necrosis

Introduction

Radiotherapy currently plays a key role in pelvic malignancies' management [1]. Excellent outcomes have been reported on its association with chemotherapy for the treatment of the anal carcinoma [2]. Despite that, the combined use of chemo- and radiotherapy [3,4] and the high doses administered [5] seem to be strongly associated with early and late onset side effects.
Radiation-induced late complications usually appear 6 to 12 months after treatment and affect 5-11% of patients [6,7]. Typical manifestations include obstructions, compromised motility, perforations, malabsorption and fistulas. Complications derive from the progressive evolution towards fibrosis and the chronic ischemia that affect and subvert the treated tissue [8,9].
These processes may be asymptomatic and undiagnosed, inevitably making the involved structures more vulnerable to additional insults [10]. How pelvic tissues may react to hypovolemic shock after radiotherapy is difficult to

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Correspondence to: Lucia Romano, MD, Department of General Surgery, Department of Biotechnological and Applied Clinical Sciences University of L'Aquila, 67100 Coppito (AQ) Italy (e-mail: lucia.romano1989@libero.it)

predict since the absence in literature, to our knowledge, of a similar combination.
In this article we report the peculiar case of a woman affected with anal carcinoma who initially underwent chemo-radiotherapy (CRT). During a follow-up magnetic resonance (MR) she developed a severe anaphylactic reaction to Gadolinium leading to a cardiac arrest. The hypovolemic shock, resulting in hypoperfusion of an organ already subjected to actinic insult, determined an intense degeneration of the pelvic tissues and subsequent development of complete rectal necrosis which required palliative surgery.

Case Report

A 72 years old woman presented to our hospital with gradual onset of pain during defecation and faecal incontinence. Some years before, the patient had undergone left ovariectomy for ovarian cyst. She referred smoking habit (about 20 cigarettes a day). Her family history was unremarkable. In July 2017 a diagnosis was made of anal squamous cell carcinoma (SCC). The clinical staging results was cT2 N0 M0, i.e. the tumor invaded the muscularis propria, without evidence of lymphadenopathy or metastasis (Fig. 1). The patient underwent mitomycin (MMC) and fluorouracil (5FU) chemotherapy, and then radiotherapy (sVMAT: Volumetric modulated arc radiotherapy). The scheduled doses were: 59Gy in 32 fractions for 7 weeks for anal lesions and 45Gy in 25 fractions for 5 weeks for lymph nodes. The response to treatment was satisfactory, with a control CT scan showing complete absence of the mass (Fig. 2). During a regular MR control, the patient developed anaphylactic reaction to Gadolinium, with shock and cardiac arrest, lasted about half an hour before she was resuscitated. After cardiopulmonary resuscitation, she was admitted in the Intensive Care Unit (ICU) in coma state, and a tracheostomy was performed.
During her stay at the ICU, due to the occurrence of a massive digestive bleeding, the patient underwent esophagogastroduodenoscopy, which reported "Bleeding gastric ulcer (large ischemic type lesion that extends from the fundus to the antrum and that bleeds over the whole area) successfully treated with Hemospray".
Her coma state lasted about 30 days, during which she was uncontactable. Then, she showed a gradual improving of her conditions, until she regained consciousness. So, after about 50 days, the patient was admitted to a Medical Department in hemodynamically stable conditions. During hospitalization, she complained about passage of stool from the vagina; so, assuming the presence of a recto-vaginal fistula, the clinicians referred her to our Surgical Department.
We decided to perform a colonoscopy, that revealed a "rectosigmoid ischemia with total necrosis of the posterior rectal wall with exposition of presacralis fascia". Also at the CT scan the communication between the rectum and the vagina was evident (Fig. 3). So, we decided to perform a Hartmann procedure: it was reported, in the middle rectum, a large ischemic necrosis, which did not make recognizable the walls of the rectum, whose anterior portion appeared in direct continuity with the vaginal lumen and whose posterior portion exclusively consisted of the presacralis fascia. Histological examination of the harvested rectal fragments revealed the presence of granulation tissue, areas of adiponecrosis and diffuse fibrous reaction up to the serosa, in absence of residual neoplastic tissue (Fig. 4). Postoperative recovery was uneventful, and the patient was discharged on post-operative day 13 in good health. No indication to the reestablishment of intestinal continuity exists.

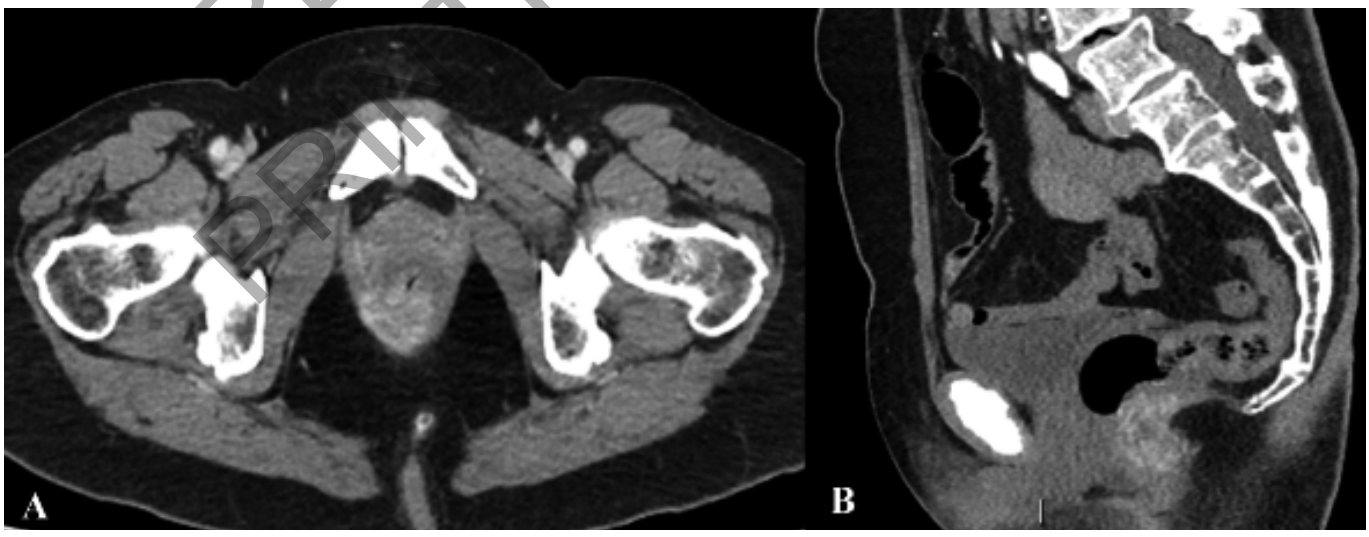

Fig. 1: Axial CT venous phase (A), with sagittal reconstruction (B), demonstrate the hypervascular mass involving the posterior wall of the anal canal, with external sphincter infiltration on the right side, referable to the primary anal neoplasm.

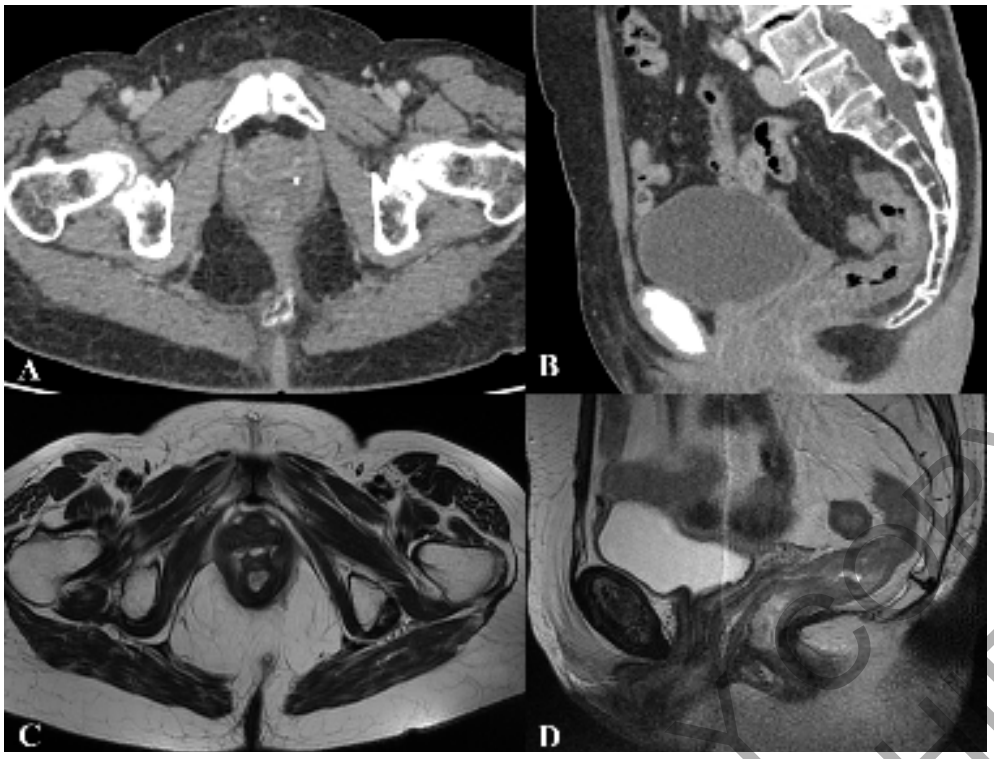

Fig. 2: After radiochemiotherapy, axial CT venous phase (A), with sagittal reconstruction (B), axial (C) and sagittal (D) MRI T2-weighted images show no abnormal mass in presence of diffuse hypointensity of anal sphincter, due to fibrosis, and mild thickening of anorectal wall, due to edema.

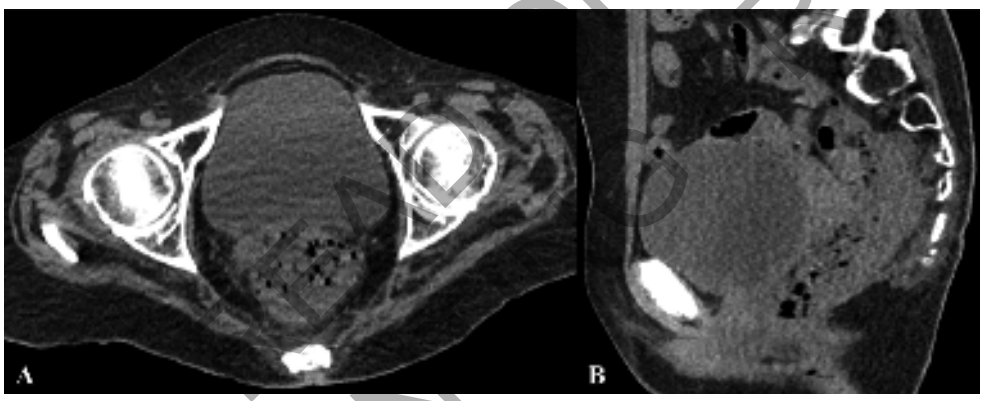

Fig. 3: Axial CT (A) without contrast, with sagittal reconstruction (B), demonstrate the communication between the rectum and the vagina with the presence of faecal material in the vaginal lumen.

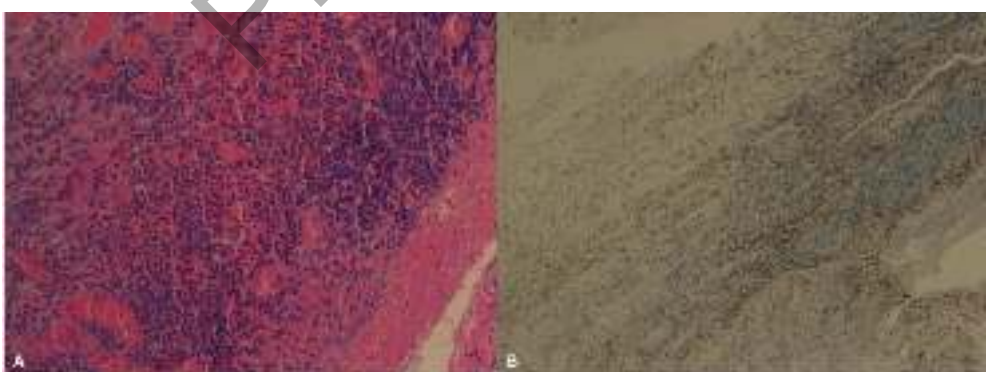

Fig. 4: Histological examination of the rectal fragments. A: presence of granulation tissue and diffuse fibrous reaction, in absence of residual neoplastic tissue (Hematoxylin and eosin staining, 20X magnification). B: Immunohistochemical CD68 expression (brown colour) highlights the presence of numerous macrophages (4X magnification).

Discussion

Before 1980 abdominoperineal resection (APR) with permanent colostomy was the standard treatment for anal cancers [11,12]. The 5-years overall survival (5yOS) ranged from 40-70% and morbidity was high [13]. Since then, several trials proved the efficacy of CRT, showing its superiority over RT alone [14-16]. Current guidelines from the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) recommend the use of CRT with 5-FU and MMC not only as neoadjuvant approach but with curative intent for local and locally advanced anal squamous cell carcinomas. This protocol is related to a 5yOS of about 78% and a rate of complete tumor regression of 80-90% [17,18]. It is considered a satisfactory result, but it is burdened, in almost all patients, by the appearance of Pelvic Radiation Disease (PRD) defined as "transient or longer term problems, ranging from mild to very severe, arising in non-cancerous tissues resulting from radiotherapy treatment to a tumor located in the pelvis" [19]. This damage is due to a direct DNA injury and also to the production of reactive oxygen and nitrogen species. In fact, these substances induce translation of several cytokines and growth factors, whose key mediator is Transforming Growth Factor-b1 (TGF-b1) [20,21].
Consequently, a fibrogenic and pro-inflammatory response occurs, leading to submucosal fibrosis and obliterative endarteritis with development of small arteries and arterioles thrombosis. Tissues become susceptible to ulcerations, fistulas formation, bleeding and ischemia, usually ending up in parenchymal hypoplasia or atrophy [22-24].
The time required for this reaction to be established and the kind and severity of these complications are quite difficult to be defined, since they depend on a host of elements such as endogenous factors, comorbidities, radiation dose and field size [25,26].
Currently, most of the studies regarding the prevention of late gastrointestinal toxicity caused by radiation induced fibrosis consider modulation of TGF-b1 and administration of free radical scavengers (such as Amifostine) but conflicting results are reported about the significance of their benefits [27,28]. Other measures include the use of expanders to keep normal tissues far from radiotherapy high dose field, obtaining satisfactory outcomes; however most of them require an invasive approach, limiting their feasibility and clinical trials[29-31]. Actual target is to prevent or minimize the onset of this inflammatory/ischemic process developing advanced radiotherapy technique, such as VMAT, reducing the surrounding normal tissue dose [32]. Nevertheless this preventive measures do not solve all problems, in fact they seem to be more effective on the onset of acute toxicity than late toxicity (this has a quote of dose-independent relationship with radiation) [19] and the overtime risk of complications requiring operative intervention is still relevant (about 4-10% over 5 years and up to 20% over 20 years for pelvic malignancies) [33-35].
In our case we faced with the rapid and severe degeneration of pelvic anatomy determined by the sum of vascular alterations following hypovolemic shock and pelvic tissues alteration after radiotherapy.
Gastrointestinal tract is highly vulnerable to ischemic injuries during hemodynamic shock, due to the disproportionate vasoconstriction of mesenteric circulation. When this occurs, gastric erosions, mesenteric non-occlusive ischemia, ischemic colitis, pancreatitis and hepatitis are expected [36,37]. What appeared remarkable in our case was how one pathogenic event produced two very different types of lesion in the same patient, such as a bleeding ischemic gastric ulcer that only required endoscopic treatment and an extended ischemic proctosigmoiditis involving almost the entire rectovaginal septum which required a surgical approach. During the surgery, the extension of the damage became evident, showing the complete absence of rectum walls and the progression of necrosis toward the sacrum in a contest of intense fibrotic reaction involving rectosigmoid junction, rectum, uterus and small bowel.
A revisal of CRT program (doses, interval between doses, check-ups) confirmed it was in accord with current guidelines and no protocol violation was revealed.

Conclusion

Considering that cancer long term survivors are increasing in number, quality of life is becoming a key aspect of the oncological radicality concept. Furthermore, a longer survival means greater possibility to develop unexpected complications due to the appearance of adverse events independent from malignancy.
The negative impact that hemodynamic shock may have on fibrotic tissues or on a vasculitis-affected microcircle (just like chemo/radio-treated tissues are) may be expected, although its intensity is unpredictable. Therefore, it seems essential not to underestimate the exponential outcome of a similar unusual combination of events, both because patients may be unresponsive or under pharmacological sedation after that (like our patient was), being unable to communicate the presence/absence of new-onset symptoms for a long time, and because an earlier diagnosis allow wider therapeutic possibilities improving quoad vitam and qouad valetudinem prognosis.

Riassunto

La radioterapia svolge attualmente un ruolo chiave nella gestione delle neoplasie pelviche. In particolare, per il trattamento del carcinoma anale, sono stati riportati esiti notevoli riguardo la sua associazione con la chemioterapia.

In questo articolo riportiamo il caso di una donna con diagnosi di carcinoma anale, trattata con chemioterapia e successivamente con radioterapia. La risposta al trattamento è stata soddisfacente, come evidenziato dalla TC di controllo che mostrava la completa regressione della massa. Durante un regolare controllo RM, la paziente ha però sviluppato uno shock anafilattico in risposta al Gadolinio, con arresto cardiaco della durata di circa mezz'ora. Dopo circa 50 giorni di ricovero in Terapia Intensiva, la paziente è stata trasferita in un reparto medico in condizioni emodinamicamente stabili. Durante la degenza, si è riscontrata presenza di feci in vagina; pertanto, assumendo la presenza di una fistola retto-vaginale, è stato disposto il trasferimento presso il nostro dipartimento chirurgico. La colonscopia ha rivelato un'ischemia rettosigmoidea con necrosi totale della parete rettale posteriore ed esposizione della fascia presacrale. Si è pertanto posta indicazione ad eseguire un intervento chirurgico secondo Hartmann. L'esame istologico dei frammenti rettali raccolti ha rivelato la presenza di tessuto di granulazione e diffusa reazione fibrosa, in assenza di tessuto neoplastico residuo.
Il verificarsi dello shock ipovolemico e la conseguente ipoperfusione di un organo già sottoposto ad insulto attinico, ha evidentemente determinato una rapida e grave degenerazione dei tessuti pelvici ed il successivo sviluppo di una necrosi rettale completa.
È noto come il tratto gastrointestinale sia altamente vulnerabile alle lesioni ischemiche a causa della vasocostrizione della circolazione mesenterica. Ciò che però appare degno di nota nel nostro caso è come un evento patogeno possa produrre due tipi molto diversi di lesioni nell'ambito dell'apparato gastroenterico: un'ulcera gastrica ischemica sanguinante che ha richiesto un trattamento endoscopico ed una proctosigmoidite ischemica con coinvolgimento dell'intero setto retto-vaginale, che ha imposto la necessità di un approccio chirurgico invasivo.

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