Reports of Practical Oncology and Radiotherapy 25 (2020) 527–532

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Case report

Adult Onset Still's Disease and Radiotherapy treatment for breast cancer: Case report about management of this rare association and literature review

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ARTICLE INFO

Article history:
Received 31 March 2019
Received in revised form 2 February 2020
Accepted 16 March 2020
Available online 22 May 2020

Keywords:
Adult Onset Still's Disease
Radiotherapy
Gating technique application
Autoimmune disease

ABSTRACT

Aim: This manuscript focuses on the first experience in literature of a patient with a complicated Adult Onset Still's Disease-related heart failure who thereafter underwent adjuvant radiotherapy for left breast cancer.
Background: AOSD is a rare autoimmune inflammation-related disease, in which life-threatening pulmonary and cardiac complications can occur. In literature, AOSD is often associated with cancer, as paraneoplastic syndrome, but there are few data about primary AOSD and management of oncological therapies.
Materials and Methods: A patient who needed adjuvant breast cancer radiotherapy underwent tumour board evaluation to define feasibility of an RT in a patient with of a history of a heart life-threatening complication 2 years before AOSD. Results of the review were discussed by a multidisciplinary panel of experts that chose the type of surgery, radiotherapy and monitoring of patient.
Results: Literature review confirmed association of AOSD with BC in some pts and uniqueness of this treatment management experience. Patient underwent RT according to schedule of 40.05/2.67 Gy/fx on residual left breast and 10/2 Gy/fx on tumour bed with the gating technique. The panel chose to keep immunosuppressive therapy with anakinra. No complications were observed at clinical, ECG and laboratory examinations. Maximum toxicity was G2 skin. At first follow up AOSD signs of flare were negative.
Conclusion: In conclusion, when oncological treatments, especially radiotherapy, are mandatory for AOSD pts, multidisciplinary management and tailored monitoring are necessary to avoid acute adverse effects and allow pts to complete therapies.

1. Introduction

Adult Onset Still's Disease (AOSD) is a rare auto inflammatory disease with unknown aetiology which can lead also to life-threatening complications. The onset of this illness is sudden and is characterized by quotidian fever, evanescent rash,

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https://doi.org/10.1016/j.rpor.2020.03.013
1507-1367/

arthritis, leucocytosis and with variable frequency abnormalities of the liver function tests, adenopathy, splenomegaly and loss of weight.[1,2] Recent advances revealed a pivotal role of several pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-18 (IL-18) in disease pathogenesis.[3]

Radiotherapy is an oncological loco-regional treatment that can promote acute inflammation on irradiated site and chronic rehash of mesenchymal tissue. In fact, radiotherapy effect on microenvironment has shown to be a promoter of IL-6 that is by itself a promoter of IL-1 and TNF-α.[4] The priming of this mechanism is linked to "damage-associated molecular pattern" in which dying tumour cells release molecules such as HMGB1 and ATP that activate pro-inflammatory genes in immune cells that induce transcription of inflammatory cytokines.[4] Their production can cause tumour cell death, increased risk of sepsis or general systemic inflammation. Inflammatory cytokines production can also cause fatigue as a systemic effect in patients who underwent adjuvant radiotherapy for breast cancer.[4]

Radiotherapy treatment is considered a possible trigger factor for activation of the pro-inflammatory cascade in some autoimmune systemic conditions including collagen and inflammatory disease, but effective absolute contraindications need to be evaluated case by case.[5,6] In literature, it is reported that clinical side effects of radiotherapy on patients with autoimmune disease can become more evident after 20 Gy.[7] There are some data regarding severe toxicities due to radiotherapy in patients with chronic inflammation, but a systematic review published by Lin et al.[6] showed that episode of G3 toxicities are, respectively, 11.7% (5.4–19.6%) and 6.1% (1.4–12.6%) for acute and late presentation, while for G4 incidence rate is respectively 1.5% and 4.5% for acute and late toxicities.[6] These data sustain the concept that radiotherapy can be safely administered also to patients with a chronic disease.[6]

Adjuvant radiotherapy for breast cancer is a consolidate therapeutic indication after breast conserving surgery, reducing 10-year risk of recurrence by 16% in respect to population not irradiated and reducing also 15-year risk of breast cancer death of 4%.[8] Frequent toxicities reported during adjuvant whole breast radiotherapy in all population of patients are acute skin toxicities and breast oedema.[9] More rare complication regards the lung and heart with a rate of sub-clinic pneumonia of up to 31%[10] and a higher risk of heart failure during follow up between 10 and 30% within 5–10 years,[11,12] In general, about heart risk, it is considered a complex and multifactorial event in which risk factors due to radiotherapy and clinical endpoints are still not clarified.[13]

In conclusion, it can be very difficult to manage complexity of pro-inflammation promotion of radiotherapy in patients with autoimmune disease or chronic inflammation. In this paper we present a case of a patient that safely underwent left breast radiotherapy after a severe heart and lung failure due to AOSD. The manuscript reports also a literature review on the association of AOSD and tumours and practical management choice by a multidisciplinary team based on scientific evidence.

2. Clinical case

A female pt of 44 years old affected by Still's disease, diagnosed in 2014 at the age of 40 years, with a life-threatening exordium with pericarditis and pleuritis, and actually in remission, had a breast cancer diagnosis in 2017.

On December 2014, she presented a cutaneous non-flat and itchy rash, localized to body and limbs. After the appearance of arthralgia in the hands and wrists, she underwent rheumatological evaluation and began therapy with prednisone with benefit. In September 2015, following suspension of steroid therapy, she developed a rash, arthralgia, myalgia and fever, with isolation of S. Hominis on bleed and auto-immunoprofile with ANA+ (1:160 with dotted pattern), FR-, anti-CCP-, ANCA-, AntidsDNA-, AntiEND-). The presence of neoplasia was ruled out with a whole-body CT scan, mammography and breast ultrasound. After the diagnosis of Still's disease (according to Yamaguchi criteria: fever >39°; arthralgia, rash, leucocytosis, abnormal liver function tests and hepatomegaly), the clinical manifestations were complicated by macrophage activation syndrome (MAS), disseminated intravascular coagulation (DIC) and pericarditis with left ventricular dysfunction (EF 20%), she underwent high-dosage cortisone, cyclosporine and intensive care interventions with inotropic infusion therapy. Considering the organ complications despite the therapies, she started also therapy with anakinra with benefit. On January 2016, she was considered hemodynamically stable and discharged from the hospital. She continued rheumatological therapy without interruption.

At the time of BC diagnosis (December 2017), the treatment with anakinra and cyclosporine were still ongoing and AOSD was considered in remission by the rheumatological consultant. Pt presents a low-grade ductal infiltrating carcinoma of 15 mm on mammography and echography at the upper-external quadrant of the left breast. Cyclosporine was suspended after the diagnosis. On January 2018, she underwent breast conserving surgery + sentinel node biopsy. No complication with wound healing were crosschecked. The final histological examination showed a ductal infiltrating carcinoma, grade 1, of 16 mm in diameter, without nodal invasion, pT1c pN0 (0/2), ER90%, PR 35%, AR 0%, Ki6715% HER2 0, FISH non amplificated. This kind of tumour usually requires an adjuvant radiotherapy treatment and endocrine therapy for at least 5 years.

On January 2018, EF was 64% and pericardial effusion was excluded at echocardiogram. Rheumatological consultation confirmed AOSD in a remission state. A tumour board evaluation (in the presence of surgeons, a radiotherapist and rheumatologist) chose to keep immunosuppressive therapy with anakira and monitor basal, weekly and then, after RT, clinical and laboratory exams to identify possible AOSD flare.

On March 2018, she underwent an adjuvant hypofractionated radiotherapy treatment for a total dose of 40.05 Gy/15 fr on the left breast and 10/5 fr Gy on the tumour bed (boost) with a gating tracking to lead thoracic wall far from the cardiac apex. For the patient, 2 simulation computed tomography scans were acquired: the first during free-breathing, and the other on prospective gating during deep inspiration breath-hold. The scans were monitored by the Varian RPM^{TM} respiratory gating system. A 3D-CRT plan was performed based on the deep inspiration breath-hold scan. Fields conformation was aimed to spare the heart and lungs. Final Mean heart dose was 1.3 Gy, V20 ipsilateral lung 12%, V30 ipsilateral lung 7% and MLD was <2.5 cm. PTV coverage was optimal according to ICRU 62.

During the treatment examination, monitoring did not show abnormalities as reported in Table 1. In addition, clinical examination did not reveal heart or lung suspicious of inflammation.

At the 4th radiotherapy daily fraction, the pt presented a H. Zoster episode on the back, far from RT fields and started oral antiviral therapy without discontinuing oncological treatment. Radiotherapy skin toxicity according to CTCAE v5.0 was erythema G2 at 44 Gy. Time for skin toxicity regression was 11 days from the end of radiotherapy. This is in line with standard expected toxicities.

Early follow up examination was negative for acute toxicities or Still's disease flare, and at 18 months from the end of RT toxicity was negative according to CTCAE v5.0.

Table 1
Patient's biochemical and instrumental monitoring during and after radiotherapy treatment. *Abbreviations*: Hb haemoglobin; PLT platelets; WBC white blood cells; NEU neutrophils; LYMP lymphocytes; MON monocytes; CRP c-reactive protein; ESR erythrocyte sedimentation rate; ECG electrocardiogram.

Monitoring exams	Week 1	Week 2	Week 3	Week 4	Follow up
Hb (g/dL)Normal values (NV): 12–15	12.3	12.4	12.9	12.4	11.3
PLT ($\times 10^9$ L^{-1}) NV: 150.0–450.0	308	315	282	190	219
WBC ($\times 10^9$ L^{-1}) NV: 4.0–10.0	9.57	7.29	8.23	5.58	6.57
NEU ($\times 10^9$ L^{-1}) NV: 2.0–7.0	6.2	3.8	4.68	3.0	3.96
LYMP ($\times 10^9$ L^{-1}) NV: 1.0–3.0	2.01	2.43	2.29	1.64	1.91
MON ($\times 10^9$ L^{-1}) NV: 2.0–10.0	0.87	0.68	0.78	0.63	7.1
CRP (mg/L) NV: <5.0	12.9*	/	/	/	0.6
ESR (mm) NV: 0–20	13	/	/	/	/
Troponine-I (ng/mL) NV: <0.040	<0.006	<0.006	<0.006	<0.006	/
NT-ProBNP (pg/mL) NV: <150	70	83	66	95	/
ECG	Normal	Low voltages of the QRS. Low progression of wave R in V1-V3. Nonspecific anomalies of the wave T	Low voltages of the QRS. Nonspecific anomalies of the wave T	Normal	Normal

Table 2
Summary reporting literature review results.

Papers matching PubMed search "adult onset still's disease" from 1975	1520
N° Case reports	645
N° Case series (<10 pts)	138
N° Case series (>10 pts)	240
N° Literature reviews	58
N° Papers excluded for their languages being different from English	44
N° Papers not available	262
N° Papers not pertinent with search	132
N° Papers with association between RT and AOSD reported	1

3. Material and methods

The authors performed a literature review using PubMed (1975–2019) to identify all studies that match with keywords "adult onset Still's disease", "AOSD", "Still disease and tumor", "Still disease and radiotherapy". Inclusion criteria were: articles that reported clinical data about the association between AOSD and tumour management, diagnosis and treatment with follow up reporting; English language of papers; complete manuscripts available. Extracted data were analyzed by dividing them according to the association between AOSD and solid tumours, haematological tumours, chemotherapy and radiotherapy.

A multidisciplinary team, consisting of a breast surgeon, radiotherapist, medical oncologist, pathologist and rheumatologist, discussed the results of literature review and clinical and therapeutic management of the patient. The key points of the discussion were: type of surgery, possible effects of radiotherapy on inflammatory pathology, management of immunosuppressant drug and ongoing monitoring of radiotherapy. Conclusions of multidisciplinary discussion are reported in the result/discussion section.

4. Results and discussion

AOSD is a rare systemic auto-inflammatory disorder, in which, despite a good management with anti-IL1 or 6, serious complications remain possible.[14,15] Aetiology of AOSD is still unknown and it's difficult to screen population at risk or to stratify pts that are at the highest risk of complications. Moreover, treatment was always empirically addressed to reduce inflammation[16] and only recently target therapies with anti-IL1 and IL6 became clinical practice.[17,18]

In literature PUBMED research, we found 1520 paper searching keywords (Table 2). The manuscripts that met the inclusion criteria were selected, reviewed and discussed by the multidisciplinary team to decide about her therapeutic pathway. First papers were published in 1975, describing clinical presentation of isolated cases. In all the search, only one case reported an association with radiation therapy, but details about monitoring or adverse effects are not reported.

4.1. Association with solid tumours

Since 1989, treatment with immunosuppressive therapies have been described,[19] but only case reports describe an association with tumour. In addition, Yamaguchi's diagnosis criteria[20] for AOSD put the malignancies among exclusion criteria because AOSD is reported as a paraneoplastic syndrome in literature. In 2015 a review reported about 30 cases of atypical AOSD presentations with malignancies, almost all BC and haematological.[21] In another review[22] that investigate AOSD and malignancies association, definition of a paraneoplastic presentation is linked to these characteristics: subsequent detection of a malignant disease was within 9 months; symptoms at a higher age, atypical features of rash, highly elevated lactate dehydrogenase, atypical cells in the differential blood count, and high concentrations of the soluble interleukin-2 receptor. In this review,[22] various categories of possible relationships between AOSD and malignancies are reported: a true paraneoplastic syndrome, a misinterpretation of tumour symptoms for AOSD, mere coincidence, or a monoclonal malignant proliferation of immune cells due to strong, initially polyclonal autoimmune proliferation, or during immunosuppressive therapy. A paper by Rogues et al.[23] reported a paraneoplastic syndrome miming Still's disease in a patient with BC. In this case, symptoms were initially resistant to high doses of steroids, and disappeared only after tumour excision, despite rapid tapering and cessation of steroid therapy. Some case reports[24,25] reported paraneoplastic manifestation as Still's Disease in women with recurrent BC after many years. Komano et al.[26] reported a case of a paraneoplastic syndrome with an AOSD pattern associated with BC diagnosis. Von Liliefeld-Toal et al.[27] in 2004 reported a case of a 52-year-old woman with diagnosis of AOSD according to Yamagouchi criteria,[20] in whom histological examination of a suspicious lymph node revealed a BC metastases and primary BC was therefore diagnosed by MR. In this woman all symptomatic patterns disappeared after surgery for BC. In another report by Routier et al.[28] paraneoplastic pseudo-Still's disease is reported associated with an undifferentiated bronchial carcinoma. Shibuya et al. in 2003 reported a case of a 77-year-old man in whomc AOSD was considered a paraneoplastic syndrome of oesophageal cancer.[29] Another case report of Mekinian et al.[30] reported an association between AOSD and subsequent diagnosis of hepatic angiosarcoma 2 years later. Anh et al.[31] in 2010 described a case of a patient diagnosed with AOSD in whom a later cervical biopsy of lymphadenopathy showed metastatic papillary carcinoma without evidence of focal lesion in the thyroid gland.

In another case associated with thyroid cancer, AOSD-like manifestation anticipated the diagnosis two month before in a 68-year-old man.[32] Yilmaz et al.[33] reported a case of a paraneoplastic syndrome AOSD-like in regression after steroids administration and associated with a sarcomatoid renal cell carcinoma. They also conduct a literature review in which the association between malignancies and AOSD was reported, concluding that since most of the reported cases were concurred with primary neoplasm or relapse, and resolved after the treatment targeted to the underlying malignancies, AOSD seems to be a paraneoplastic syndrome. A similar case of paraneoplastic AOSD-like syndrome that anticipated ovarian cancer diagnosis is reported in literature.[34] As in the previous cases, diagnosis was concomitant to biopsy of lymphadenopathy developed during AOSD-like symptoms developing. In 2015, Yang et al.[35] reported a case of piriform sinus carcinoma accompanied by a paraneoplastic syndrome that was initially misdiagnosed as Adult Onset Still's Disease. A case of a thymoma is reported in literature after four years of therapy with anakinra for AOSD, with an interpretation of a possible deregulation of immunity leading to oncogenesis.[36]

4.2. Association with haematological malignancies

Literature indicates that Still's disease can anticipate some lymphoma[37–44] or leukaemia cases.[45–49] In an HIV patient treated with methotrexate (MTX) for AOSD, a case of lymphoproliferative disorder arising in the right maxillary molar region was described.[50] In literature a presentation with leukemic reaction in a patient with Down Syndrome during AOSD is also described.[51]

4.3. Association with chemotherapy

Regarding the association with oncological treatment, Bosch-Barrera et al.[52] reported in 2009 a case of toxicity with AOSD exordium after the 1st cycle of chemotherapy with pemetrexed and gemcitabine in a patient with non-small cell lung cancer. In 2011 a case report of Wu et al.[53] described a 56-year-old patient with advanced lung adenocarcinoma who developed a remittent fever together with pharyngodynia and joint pain after the first cycle of chemotherapy with paclitaxel plus carboplatin; the patient was diagnosed as AOSD-like paraneoplastic syndrome. On the contrary, a benefit of chemotherapy administration on macrophage activation syndrome (MAS) due to AOSD is reported in a patient who underwent treatment with etoposide and doxorubicin.[54]

4.4. Association with radiotherapy

About radiotherapy association, a case is reported of a man undergoing AOSD therapies who was diagnosed of carcinoma with sarcomatoid element (CSE) in the mediastinum and underwent 50 Gy radiotherapy, but there are no considerations about long-term effects as his condition gradually worsened, and the patient died.[55]

4.5. Patient's management

After literature review, the Multidisciplinary Team discussed the possibility to treat this patient at diagnosis. Key-points of the decision process were:

- AOSD aetiology is unknown, probably it has a cytokine-related origin;
- The disease was in remission at the time of BC diagnosis and probably the exordium with high fever was pathognomonic of a monocyclic disease[56];
- IL-1 inhibitor (anakira) was ongoing with benefit on clinical and lab exams;
- The mastectomy could have been very invasive and the healing process, which also included the reconstruction, could act as a trigger for the reactivation of Still's disease;
- Radiotherapy can hypothetically change cytokines and chemokines secretion and influence the inflammatory status. In particularm RT can enhance the production of both pro-inflammatory (IL-6, IL-8, IL12p70, TNF-α, INF-γ, IL-1α) and immunosuppressive factors (IL-10, IL-1β, and reduction of VEGF and TGF-β).[57] We evaluate that, after all, our patient was under IL-1ra, so the equilibrium was more towards global immunosuppression and in case of exacerbation of inflammation we could use steroids to suppress activation;
- New radiotherapy technologies could preserve the heart in order to reduce pericarditis risk, in fact women population treated with radiotherapy for BC presents not only the risk of developing ischaemic heart disease, but also pericarditis and valvular disease[58];
- During treatment, we could monitor heart function with ECG and troponin[59] and pro-BNP blood dosage.

For radiotherapy schedule choice, results on acute toxicities reported from major trials showed that a standard fractionation had a higher incidence of grade 2 and 3 of any district,[60,61] In these trials, also the long-term analysis confirmed that START B presented low rates of ischaemic heart disease (1.1%) and pneumonitis (0.5%), with no differences with hypofractionation. In addition, also evaluating late toxicity profile on the muscle-skeletal system, in the hypofractionation group no acute and late soft tissue necrosis was not reported, and also fibrosis of the superficial and deep connective soft tissue was not significantly higher than in standard group.[60] For these reasons, and also to reduce overall time of treatment and exposure to inflammatory trigger, we chose to use hypofractionation schedule according to the START B protocol[62] and also ASTRO guidelines.[63]

Although, therefore, an immune reactivation due to the inflammation of radiotherapy could be expected, there have been no episodes of increase in the indices of inflammation, nor of pericarditis or pleuritic. Further evaluations could be interesting to investigate about late toxicities presentation in this patient in terms of skin fibrosis, pericarditis and lung injury. In contrast, the patient presented an episode of Herpes Zoster, probably related to immunosuppressive therapy. In literature,[64–68] association with herpes zoster was already described, as in our clinical case presentation of flare during AOSD can be frequent. In addition, the weekly cutaneous toxicity was superimposable to that of the normal irradiated population. Longer follow up is necessary to understand if this case is a monocycle or polycycle presentation in which radiotherapy treatment or eventually BC relapse could play a role in AOSD representation.

4.6. Evidence for clinical monitoring

The patient underwent a monitoring during RT with ECG, troponin dosage and pro-BNP. The literature reports that c-reactive protein CRP is associated with heart failure and is a surrogate of cytokines linked to inflammation.[69] CRP is also a marker of prognosis for pts who underwent heart failure.[69] In addition, several studies report that during radiotherapy troponin I and NT-ProBNP can be considered early markers of heart injuries.[12] In particular, about dosimetric correlation, NT-ProBNP monitoring with values under 125 pg/mL is usually associated with V_3 of 18.9% of the heart and V_2 of 77.5% of the ventricle[70]; instead, it is reported that troponin I remains usually stable also in case of NT-ProBNP alterations in the function of V3 and V2.[66] These studies suggest that for V3 and

V2 are exceeded in patients who are candidate to RT and at risk of acute heart failure, NT-ProBNP is a sensible marker for injuries and can be used for monitoring. In our case report, we checked heart V3 and ventricle V2 after plan elaboration and they were respectively 12.6% and 54%. These values are in line with normal clinical and lab findings during monitoring of the patient.

5. Conclusion

To our knowledge, this is the first experience in literature of a patient with complicated life-threatening AODS-related heart failure who underwent adjuvant radiotherapy to the left breast without unexpected side effects. Further evaluations are necessary to assess also late toxicities. In conclusions, when it is mandatory to address pts with Still's disease to oncological treatments, especially radiotherapy, it is important to tailor adequate monitoring to avoid acute adverse effects and allow pts to complete the treatments. In particular, heart V3 and ventricle V2 under constraints are related to normal lab and clinical findings.

Compliance with ethical standards

This study was conducted without funding. All the authors have no conflict of interest to declare. All procedures performed in the study were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from participant included in the study.

Established facts and novel insights

Established facts
- Adult Onset Still's Disease (AOSD) is an autoimmunity disease that can also occur concomitant to cancer diagnosis
- Radiotherapy (RT) could potentially enhance inflammatory mechanisms to AOSD flare throughout activation of inflammatory cytokines cascade

Novel insights
- It is feasible to treat patients (pts) with RT after AOSD, also with previous life-threatening complications
- An adequate multidisciplinary monitoring of possible flare of AOSD during RT should be adopted
- Immunosuppressive drugs should be continued during RT

Conflict of interest

None declared.

Financial disclosure

None declared.

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