



Frequency and outcome of SARS-CoV-2 infection in patients with adrenocortical carcinoma followed at a reference center in Italy

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Received: 27 July 2020 / Accepted: 22 November 2020 / Published online: 5 January 2021
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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection rapidly expanded and swiftly led to a public health crisis worldwide.

Cancer patients infected by SARS-CoV-2 are at greater risk for severe illness and related death than general population, depending on primary malignancy, disease stage and type of treatment received [1–3].

Adrenal cortical carcinoma (ACC) is a rare endocrine malignancy which has several peculiarities compared to the other malignancies: (1) ACC may produce steroid hormones in over 50% of cases, (2) most ACC patients are treated long term with mitotane, an adrenolytic drug which requires steroid coverage; (3) ACC patients with advanced disease are often treated with mitotane associated to chemotherapy which leads to additional immunosuppression [4]. All these features place ACC patients potentially at high risk of SARS-CoV-2 infection and relevant complications. No data are up to now available on frequency and outcome of SARS-CoV-2 infection in ACC patients.

The medical oncology of the Azienda Socio-Sanitaria Territoriale-Spedali Civili of Brescia is a referral center for ACC in Italy. It is located in Lombardy, the Italian region that recorded the highest number of people infected with the

virus. This retrospective monocentric study was undertaken to provide data on whether ACC patients are at greater risk of contracting SARS-CoV-2 infection than patients with other malignancies and the general population, and whether the viral infection in ACC patients has a worse prognosis.

During the Coronavirus disease (COVID-19) pandemic, 92 ACC patients were followed at the Brescia Oncology Unit. They were 36 (39.1%) males and 56 (60.9%) females, median age 55 years (range 23–83), of whom 49 (53.2%) patients have been radically operated and were free of disease. Twenty-three of them (46.9%) were on adjuvant mitotane therapy [5]. Among the 43 patients with metastatic disease, 25 (58.1%) were treated with mitotane, 18 (41.8%) were receiving chemotherapy + mitotane as follows: first line EDP (Etoposide, Doxorubicin, Cisplatin) [6] in 8 patients; second/third line therapies with temozolomide [7] in 5 patients (4%) and gemcitabine-capecitabine [8] in 5 patients (5%). Forty-seven patients (51.1%) were resident in Lombardy while the remaining 45 lived in the rest of Italy.

Six ACC patients (6.5%) developed COVID-19 symptoms, five of them resident in Lombardy. The frequency of symptomatic SARS-CoV-2 infection in ACC patients living in Lombardy was as high as 10.9%. In the same period, 1163 cancer patients with breast, lung, gastrointestinal, head and neck, melanoma and sarcoma primary malignancies received antineoplastic therapies at the Brescia Oncology Unit, which consisted in chemotherapy (50.1%), immunotherapy (13.4%) and molecular target therapies (36.5%). Twenty-nine patients (2.5%) developed symptomatic SARS-CoV-2 infection and 8 of them (27.0%) died.

As shown in Table 1, all ACC patients developing COVID-19 symptoms were receiving mitotane at a dose ranging between 0.5 and 6.0 g daily. Mitotane was prescribed in adjuvant setting in 5 patients, while it was administered in association with temozolomide, at the dose of 250 mg daily for 5 days every 28, in the remaining patient. In all patients, except one, serum mitotane levels were below the therapeutic range (14–20 mg/L) [9], due to

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Table 1 Characteristics of ACC patients developing COVID-19 symptoms

ID	Sex	Age (years)	Secretory Status ^a	Antineoplastic Therapy	Disease Stage	Comorbidities	Mitotane treatment and last Mitotane level	Mitotane start	Hormone Assessment [normal range]	Symptoms at the time of hospital admission or at naso-pharyngeal swab	Steroid replacement and modifications during COVID19 infection	Radiological evaluation	COVID19 Therapy	Outcome
1	F	61	Cortisol	M	Radical resection Adjuvant setting	-	1000 mg/day 8.8 mg/L	August 2017	Cortisol: in range UFC: in range Androgens and precursors: below normal range Aldosterone: in range	Fever, dyspnea, cough	Hydrocortisone 300 mg e.v./day during hospitalization. Then habitual dose of 25 mg/day	Lung interstitial disease	Hydroxychloroquine, azitromycin, antiviral, non-invasive oxygen support (13 days) (inpatient)	Full recovery
2	F	31	Androgen	M	Radical resection Adjuvant setting	-	Withdrawn from December 2019 4.5 mg/L	February 2019	Cortisol: below normal range UFC: 213 ug/24 h [5.8–61.6] Androgens and precursors: below normal range Aldosterone: in range	Fever, cough, asthenia, anosmia, ageusia	Hydrocortisone 100 mg i.m./day for 4 days in addition to habitual dose of cortone acetate 75 mg/day. Then habitual dose	-	Quarantine (15days) (outpatient)	Full recovery
3	M	62	None	M	Radical resection Adjuvant setting	Hypertension, myocardial infraction	3000 mg/day 13.4 mg/L	May 2019	Cortisol: in range UFC: in range Androgens and precursors: in range Aldosterone: in range Renine: in range	Fever, cough, asthenia	Cortone acetate 100 mg/day for 5 days and then his habitual dose of 75 mg/day	-	Quarantine (15days) (outpatient)	Full recovery
4	F	72	Androgen	M	Metastatic disease 1 st line therapy	HCV +, hypertension, hypercholesterolemia	3000 mg/day 3 mg/L	March 2020	Cortisol: in range UFC: in range Androgens: testosterone 2.9 ug/L [0.03–0.41], androstenedione 1.78 ng/mL [0.5–2.5], DHEAS 7.8 ug/mL [0.8–5.6] Aldosterone: in range Renine: 66 uU/mL [4.4–46]	Fever, cough, asthenia	Cortone acetate 72.5 mg/day for 2 days and then habitual dose of 62.5 mg/day	-	Quarantine (20days) (outpatient)	Full recovery
5	F	28	Cortisol	M + TMZ	Metastatic disease Heavily pretreated	-	1000 mg/day 21.0 mg/L	March 2019	NA	Fever, dyspnea	Hydrocortisone 250 mg e.v. daily during hospitalization. (Habitual dose before hospitalization: cortone acetate 50 mg/day)	Lung interstitial disease	Invasive oxygen support (15days) (inpatient)	SARS related Death
6	F	30	None	M	Radical resection Adjuvant setting	-	1500 mg/day 10.3 mg/L	July 2019	Cortisol: below normal range UFC: in range Androgens and precursors: in range Aldosterone: in range	Mild fever	Unchanged. Habitual dose: cortone acetate 50 mg/day	-	Quarantine (15days) (outpatient)	Full recovery

^aAt diagnosis

COVID-19 Coronavirus disease 19, HCV hepatitis C virus, M mitotane, SARS Severe Acute Respiratory Syndrome, TMZ temozolomide, UFC urinary free cortisol excretion

patient intolerance/compliance, end of therapy, or mitotane therapy prescribed for <3 months. Steroid supplementation consisted of cortone acetate, which was administered at the median dose of 56.2 mg daily (range 25.0–75.0). All patients have been tested positive at reverse transcription-polymerase chain reaction on nasopharyngeal swab samples. Mitotane was suspended until complete symptom resolution and naso-pharyngeal swab became negative, while steroid supplementation was maintained and increased in patients with fever. Four patients developed mild or moderate COVID-19 related symptoms, i.e., sore throat, nasal congestion, muscle pain, diarrhea, anosmia, dysgeusia, fatigue. None of them had severe dyspnea. These patients remained in quarantine at home for 15–20 days. Two patients were hospitalized for acute interstitial pneumonia and one of them died in the intensive care unit, due to acute respiratory distress syndrome (ARDS). This patient was the youngest in the studied group, she had multiple metastatic lesions in lung and liver and was receiving mitotane plus temozolomide therapy as second line approach after disease progression to EDP. The last blood count, performed 5 days before hospital admission due to SARS-CoV2 related respiratory impairment, revealed neutropenia G1 and lymphopenia G2, according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0). The proportion of COVID-19 related death in our small series of ACC patients was 1 out of 6 (17.0%).

From this small series some considerations could be drawn. Firstly, ACC patients seemed to be at higher risk of symptomatic infection in comparison with both the general population and cancer patients bearing other malignancies. Secondly, SARS-CoV-2 infected ACC patients did not appear to be at increased risk of death than cancer patients with other histologies who contracted the virus. Thirdly, symptomatic SARS-CoV-2 infection occurred only in ACC patients under mitotane, regardless of the stage of the disease. Mitotane causes hypoadrenalism and requires a replacement therapy, which is tapered empirically on clinical basis and is therefore imprecise. Thus, steroid replacement may result in either hypo- or hypercortisolism and both these conditions could predispose to SARS-CoV-2 infection [10, 11]. In a recently published retrospective study on 121 patients with Addison's disease under steroid supplementation, only 1 of them (0.8%) developed COVID19 [12]. It seems therefore that hypoadrenalism associated with ACC under treatment with mitotane could be associated with a higher frequency of COVID 19 than hypoadrenalism resulting from non-neoplastic diseases. On the contrary, ACC patients seemed to share the same risk factors of death that other cancer patients. All these data however need confirmation, due to the small number of ACC patients considered. Noteworthy, mitotane serum levels was within the therapeutic range in only one out of

six ACC patients developing COVID19. These data suggest mitotane per se may have not contributed to the onset of symptoms. Indeed, the patient who died, due to extensive pneumonia and ARDS, had a metastatic disease with a heavy tumor load and was receiving temozolomide in association with mitotane and steroids. Temozolomide frequently induces lymphopenia [7] and this condition has been shown to be associated with poor prognosis in patients undergoing SARS-CoV2 infection [13]. Both the advanced stage and the documented drug induced lymphopenia could have contributed to the poor outcome of SARS-CoV-2 infection in this patient.

Moreover, symptomatic SARS-CoV-2 was mainly confined among patients who were resident in Lombardy, this observation suggests the adoption of strict preventive measures by ACC patients, who are more vulnerable since they are frequently on steroid supplementation, in areas at high incidence SARS-CoV-2 infection. Telemedicine, which uses telecommunications technology to deliver health care at patient home, represents undoubtedly an indispensable tool in the management of cancer patients in the SARS-CoV-2 pandemic, including endocrine cancers [14], since it has demonstrated to be equivalent to in-person care [15]. More generally, the approach to the patient with ACC should change in the COVID era and every therapeutic choice, such as the decision to start adjuvant mitotane in radically operated patients, or EDP-M in case of advanced disease, should be adopted taking into account the infectious risk and relevant complications in the cost / benefit assessment.

Our patient series is small, retrospective, and was not systematically screened for SARS-CoV-2. These are major limitations of this study. We cannot exclude that a number of subjects could have been infected while remaining asymptomatic or mildly symptomatic [16].

Based on these preliminary data, a European Network for the Study of Adrenal Tumors (ENS@T) study, aiming to assess the frequency and outcome of SARS-CoV-2 infection in ACC patients managed at different reference centers worldwide, is currently under way.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Deborah Cosentini, Salvatore Grisanti, Marta Laganà, Vittorio Domenico Ferrari, Alberto Dalla Volta. The first draft of the manuscript was written by Deborah Cosentini, Salvatore Grisanti and Marta Laganà. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors received no financial support for the research and authorship.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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