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Outcomes of patients with cancer and sarcoid-like granulomatosis associated with immune checkpoint inhibitors: A case-control study

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1 **Outcome of patients with cancer and sarcoid-like granulomatosis associated with**
2 **immune-checkpoint inhibitors: a case – control study.**

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51

52 **ABSTRACT (307 words)**

53 **PURPOSE:** Sarcoid-like granulomatosis (SLG) reaction caused by immunotherapy remains
54 poorly understood. This study aims to investigate the outcome of patients with cancer and
55 SLG associated with immunotherapy.

56 **PATIENTS AND METHODS:** Between April 2016 and June 2020, 434 patients with
57 immunological adverse events were screened from the ImmunoTOX assessment board of
58 Gustave Roussy, academic cancer center in France. Among them, 28 patients had SLG
59 associated with immunotherapy (SLG cohort) and 406 patients had other immunological
60 adverse events (control cohort). Clinical characteristics and outcome of patients were
61 compared from SLG and control cohort.

62 **RESULTS:** The SLG cohort consisted of 28 patients, 14 women and 14 men, with median
63 (range) age of 56.5 (28.7-75.3) years. Patients in SLG cohort with sarcoidosis were
64 asymptomatic (only radiographical finding) in 13 (46.4%) cases, otherwise most frequent
65 symptoms were dyspnea in 8 (28.6%) patients and cough in 5 (17.8%) patients. The
66 computerized tomography scan found sarcoidosis localizations in mediastinal or peri-hilar
67 thoracic lymph nodes in 26 (92.9%) patients and lung parenchymal involvement was found in
68 14 (50.0%) patients. The radiographic Scadding stages for sarcoidosis classification was
69 distributed in stages 0, I, II, III and IV in 2 (7.1%), 13 (46.4%), 11 (39.3%), 1 (3.6%) and 1
70 (3.6%) patient, respectively. Compared to patients with other immunological toxicities (cohort
71 control), patients with sarcoidosis presented most frequently with melanoma (75.0% versus
72 21.9% of patients; $p < 0.001$) and more often, received combined therapies of anti-PD1 plus
73 anti-CTLA4 (46.4% versus 12.6% of patients; $p = 0.002$). Patients with sarcoidosis had an
74 improved overall survival (OS); median OS were not reached in SLG cohort and 40.4 months
75 in control cohort, $HR = 0.232$ [95%CI: 0.086-0.630] ($p = 0.002$).

76 **CONCLUSION:** Sarcoidosis-like reactions in patients receiving immunotherapy were
77 reported as non-severe immunological reactions in most cases and were correlated with
78 improved overall survival. Sarcoid-like granulomatosis should not be misdiagnosed as tumor
79 progression in patients receiving immunotherapy treatment for cancer.

80

81 **Keywords:** Sarcoidosis; immune checkpoint inhibitor; immune-related adverse events

82

83 **(3909 words)**

84

85 **INTRODUCTION**

86 Sarcoidosis is a systemic disease characterized by granulomatous lesions in the
87 lymph nodes, lungs, and other organs with a prevalence ranging from 4.7 to 64.0 per
88 100,000 persons, and an incidence ranging from 1.0 to 35.5 per 100,000 cases per
89 year (1). Sarcoidosis is more common in Northern European and African American
90 populations and is less common in Japan (1). Sarcoidosis is more frequent in women
91 with a female to male ratio of 1.20:1.75. The average age of patients at diagnosis is
92 48 years. (1,2)

93 Sarcoidosis commonly involves the lungs and thoracic lymph nodes with an
94 interstitial parenchymal involvement that could eventually lead to lung fibrosis, in
95 more severe cases. Other common organs affected by sarcoidosis are skin, eyes,
96 bones, liver, spleen, heart, upper respiratory tract, salivary glands, and the central
97 nervous system. Importantly, sarcoidosis could also be presented as a mild illness
98 disease, and incidentally discovered by imaging in asymptomatic patients (3).

99 The diagnosis of sarcoidosis is generally suspected on typical radiological findings
100 with thoracic peri-hilar lymph nodes, of non-compressive and symmetrical aspects.
101 For the formal diagnosis of sarcoidosis, histological confirmation is required showing
102 noncaseating granulomas lesions on lymph nodes or upper tract respiratory or
103 salivary glands (4).

104 Sarcoidosis origin of disease is regarded as the consequence of a chronic and
105 dysregulated immune response by environmental factors and in subjects with a
106 genetic susceptibility, leading to granulomas constitution in lymph nodes and normal
107 tissues, possibly triggered (4). Several studies have also shown a potential link

108 between sarcoidosis and cancer occurrences such as melanoma and Hodgkin
109 lymphoma, discussing sarcoidosis as a possible paraneoplastic condition (5,6).
110 Some drugs could also be associated with sarcoidosis causality, the so-called drug-
111 induced sarcoidosis-like reactions. The common classes of drugs involved were
112 antiretroviral therapies, interferons and tumor necrosis factor antagonists (7). More
113 recently, some case reports of granulomatosis associated with immune checkpoint
114 inhibitors (ICIs) were reported (8–10) and ICI were added to the list of drug-induced
115 sarcoid-like granulomatosis reactions (11).
116 Sarcoidosis associated with immunotherapy remains an infrequent and poorly
117 understood complication associated with immunotherapy and probably
118 underdiagnosed as biopsies for histological confirmation of sarcoidosis are not
119 systematically perform (12). Only a few cases and limited series of patients so far
120 been reported (12–14). In this case-control study, objective was to investigate and
121 describe the clinical, radiological characteristics and outcome of patients with cancer
122 and sarcoidosis associated with immune checkpoint inhibitors.

123

124 **METHODS**

125 • **Study design and patients' selection.**

126 The study design was descriptive, observational, with no examination or drug
127 interventions. A case-controlled study compared patients with sarcoidosis associated
128 with immunotherapy and included the so-called sarcoidosis like granulomatosis
129 (SLG) cohort, to patients with other immunological complications of immunotherapy
130 (control cohort). The inclusion criteria for the SLG cohort were all adult patients (18
131 years or older), included in the ImmunoTOX registry conducted by Gustave Roussy
132 Institute, and having had a development of a sarcoidosis reaction proven
133 histologically and related to immunotherapy by immune checkpoint inhibitor. The

134 criteria for inclusion in the control cohort were all adult patients (18 years or older),
135 included in the ImmunoTOX registry conducted by Gustave Roussy Institute, and
136 who developed an immune-related adverse event with immune checkpoint inhibitor
137 immunotherapy other than sarcoidosis reactions. This study is academic,
138 retrospective, and collected real-life data of clinical, radiological and outcome of
139 patients treated by immunotherapy at Gustave Roussy, anti-cancer center in France.
140 The SLG patients' cases were screened among the academic toxicity of
141 immunotherapy assessment and management board of Gustave Roussy, called
142 ImmunoTOX (15). The ImmunoTOX committee is a collaborative organization of
143 immunological toxicology management at Gustave Roussy, and composed of
144 oncologists, internal medicine practitioners, pharmacovigilance pharmacists,
145 supportive care specialists, radiologists, lung specialists and other organ specialists,
146 aimed at supporting the clinical management of patients with immunological toxicities
147 (15). All requests submitted to the ImmunoTOX board of patients who received ICI for
148 the treatment of cancer between April 2016 and June 2020, were screened for this
149 study. During the study period, 577 patient requests were sent to the immunoTOX
150 board, among them 434 were confirmed with immunological toxicities. Among the
151 434 patients with immunological toxicities, 28 patients with sarcoidosis associated
152 with immunotherapy were identified and were included in the sarcoid-like
153 granulomatosis cohort, the remaining 406 patients with other immunological toxicities
154 were included in the control cohort (*figure 1*).

- 155 • **Definition for sarcoid-like granulomatosis and other immunological**
156 **toxicities.**

157 Histological confirmation with granulomatosis in patients treated with immune
158 checkpoint inhibitor was required for the inclusion of patients in the SLG cohort. The

159 clinical data from patients with a histologically proven SLG were then retrospectively
160 collected and compared to patients with other immunological toxicities (control
161 cohort). The localizations of sarcoidosis was calculated according to the World
162 Association of Sarcoidosis and other Granulomatous Disorders classification (4).
163 Immunological toxicities were defined as any immune-related complication or
164 adverse event of immunotherapy. The causal nature of the relationship between the
165 administered immunotherapy and immunological toxicity was classified as "certain",
166 "probable", "possible", "unrelated", "unclassified", or "unclassifiable" according to the
167 World Health Organization's system for standardized case causality assessment
168 (16). In the study, an immune-related adverse event (irAE) was defined here as an
169 adverse event related to immunotherapy by immune checkpoint inhibitor and whose
170 relationship to therapy was "certain", "probable" or "possible".

171 • **Computerized tomography scan acquisition and radiological central**
172 **reviewing.**

173 Retrospective X-ray analysis of serial chest computerized tomography (CT) scan of
174 all patients in SLG cohort were centrally reviewed by two expert radiologists (S.A.
175 and Co.B.), who investigated the radiological features of sarcoidosis and evaluated
176 Scadding radiographic stages (17). The best radiological anti-tumor response with
177 immunotherapy was centrally reviewed and reported in patients of SLG cohort
178 according to i-RECIST V1.1 (18). Previous chest CT scans before the initiation of
179 immunotherapy were reviewed for all patients in SLG cohort, to identify a previously
180 undiagnosed sarcoidosis. The CT scans were performed according to the treating
181 physician discretion, every 2 to 3 months. All CT scans analyzed had a high-
182 resolution CT algorithm to be comparable with each other. Other diagnostic imaging
183 procedures such as positron emission tomography (PET) scans were analyzed, when

184 performed in SLG cohort, and centrally reviewed by an expert radiologist (SA). 18F-
185 FDG PET and CT-scan acquisitions whole-body CT scan acquisitions were
186 performed using a 64 Hi-according to local institution guidelines. For images
187 acquisitions, speed spiral scanner (GE Medical Systems, Milwaukee, WI) technology
188 was used after infusion of contrast product intravenously, according to local institution
189 guidelines.

190 • **Patient's data collection.**

191 In SLG and control cohorts, clinical characteristics of patients and outcome with
192 overall survival data were retrospectively collected for all patients from electronic
193 medical records within Gustave Roussy. In SLG cohort, all biopsy samples of
194 sarcoidosis were centrally reviewed by an expert pathologist (VTDM). The treatment
195 of sarcoidosis was left at the discretion of the referring physician. Management of
196 patients with sarcoidosis was collected as well as immunotherapy continuation or
197 cessation.

198 • **Statistical analysis**

199 Data were quoted as the median (range), the median [interquartile range (IQR)], or
200 (for data on survival) the median [95% confidence interval (CI)]. Severity of
201 immunological adverse events of immunotherapy were assessed according to the
202 CTCAE v.5 scale. Qualitative variables were reported as the frequency (percentage)
203 and compared using chi-squared or Fisher exact tests. Quantitative variables were
204 compared using a non-parametric Mann-Whitney test. The threshold for statistical
205 significance was set to $p < 0.05$. Overall survival (OS) was defined as the time interval
206 between the first administration of the immune checkpoint inhibitor and death from
207 any cause. Survival data were calculated by the Kaplan-Meier method and compared
208 using a log-rank test. Hazard Ratios (HRs) were calculated with a Cox model in

209 univariate analyses. For multivariate analysis, the effect on OS for variables with a
210 significant difference between the two cohorts (SLG and control cohorts) was
211 calculated. Overall survival analyzes compared the outcome of patients with
212 sarcoidosis (SLG cohort) and without sarcoidosis (control cohort) and were carried
213 out in the entire population with all tumor types and in patients with melanoma. The
214 variables with a log rank $p < 0.2$ in univariate analyses were included in the primary
215 model for the multivariate analysis. The R[®] software version 3.6.1 was used for the
216 statistical analyses. All the patients gave their verbal informed consent to provide
217 their anonymized data, and the study was approved by the institutional review board
218 at Gustave Roussy Cancer Campus (Villejuif, France), and was registered with the
219 French National Data Protection Commission (the reference number *at Commission*
220 *Nationale de l'Informatique et des Libertés* was: 2098694v0).

221 **Role of the funding source.**

222 This study was funded by Gustave Roussy as part of the Gustave Roussy
223 Immunotherapy Program. This dedicated institutional program (launched in 2015)
224 was designed to accelerate the clinical development of immunotherapy and to
225 strengthen translational research, so that as many patients as possible can benefit
226 from novel immunotherapeutics. The funding source had no influence on the data
227 collection or the presentation of the results. The investigators CC, CP, SA, ALV, OL,
228 AM, and JMM had full access to the raw data. All authors approved the final version
229 of the manuscript. The corresponding author had full access to all data in the study
230 and had final responsibility for the decision to submit the manuscript for publication.

231

232 **RESULTS**

233 **Clinical characteristics of patients.**

234 Overall, 28 patients were included in the SLG cohort and 406 patients with other
235 immunological toxicities were included in the control cohort. The detailed
236 characteristics of patients with SLG and other immunological toxicities were
237 summarized in **table 1**. The average age of patients tended to be younger in the SLG
238 cohort compared to the control cohort (median age of 56.5 versus 63.1 years;
239 $p=0.052$). More often, patients in the SLG cohort, tended to have a medical history of
240 autoimmune disease before commencing immunotherapy treatment (14.3% versus
241 4.9%; $p=0.061$). In the SLG cohort, 4 patients with a history of autoimmune disease
242 had thyroiditis, Crohn's disease, sarcoidosis, Guillain-Barre syndrome (one patient for
243 each disease). Compared with control cohort, more patients with skin cancer were
244 identified (75.0% versus 23.2%; $p<0.001$) and less patients with lung cancer (0%
245 versus 30.8%, $p<0.001$) in SLG cohort. Patients in SLG cohort received a
246 combination of immunotherapy treatments, anti-PD1 plus anti-CTLA4 (46.4% versus
247 12.6%; $p=0.002$) more frequently.

248 **Characteristics of sarcoidosis in SLG cohort.**

249 *Pathological findings with granuloma characteristics.* According to study criteria,
250 histological confirmation of sarcoidosis was obtained for all 28 patients in SLG cohort.
251 Histopathological results were consistent with epithelioid and gigantocellular
252 granulomas without necrosis in all patients. Histopathological results were obtained
253 from biopsies of mediastinal lymph node (n=19 patients including 18 by
254 endobronchial ultrasound and 1 by mediastinoscopy), kidney biopsy (n=2 patients),
255 skin biopsy (n=2 patients) and liver biopsy (n=2 patients), bronchial biopsy (n= 1
256 patient), lung biopsy (n= 1 patient), subdiaphragmatic lymph node (n=1 patient).
257 *Time to sarcoidosis diagnosis.* The median (range) time from immunotherapy
258 initiation to sarcoidosis histological diagnosis was 5.1 (1.5-31.5) months (**table 2**).

259 The median (range) time from immunotherapy initiation to sarcoidosis first
260 radiological abnormalities observed was 2.8 (1.0-29.3) months (**table 3**).

261 *Clinical characteristics.* According to the World Association of Sarcoidosis and other
262 Granulomatous Disorders classification (4), patients had a median (range) of 2 (1-4)
263 localizations of sarcoidosis. The main organs involved by sarcoidosis were the
264 thoracic and mediastinal lymph nodes (n=26; 92.9%), lungs (n=14; 50.0%) and skin
265 (n=3; 10.7%). Skin sarcoidosis symptoms were identified in 3 patients (11%), scar
266 sarcoidosis in two patients, and oral sarcoidosis aphthosis in 1 patient. Fifteen (53.6%)
267 patients were symptomatic for sarcoidosis and most common symptoms were
268 dyspnea (n=8; 28.6%) and cough (n=5; 17.8%).

269 Severity of sarcoidosis evaluated with CTCAE was mild to moderate (grade 1-2) in 26
270 (92.9%) patients, and more severe (grade 3) in two patients (7.1%). With a median
271 (range) follow-up of 31.6 months (ranging from 6.3 to 60.3 months) in SLG cohort
272 from sarcoidosis diagnostic, four patients died due to cancer progression, no patients
273 died due to sarcoidosis (**table 2**).

274 *Laboratory tests.* All patients in SLG cohort had complete standard chemistry tests
275 including serum creatinine, calcemia and liver tests, and their results are summarized
276 in **table 3**. No hypercalcemia was observed. Eleven patients had creatinine increased
277 over the upper normal value, in 2 patients related to sarcoidosis (kidney biopsy
278 revealing granulomatous lesions). Two patients had grade 3 increased
279 transaminases related to sarcoidosis, in these two patient's enzymes hepatic
280 increase was predominant on ALT over AST. The serum angiotensin converting
281 enzyme (ACE) was elevated in four of ten (40.0%) patients tested.

282 *Respiratory tests.* In SLG cohort, respiratory functional tests (RFT) and bronchoscopy
283 were performed in 19 patients (**table 3**). Overall, RFT were found abnormal due to
284 sarcoidosis in 8 (28.6%) patients consisting of reduced carbon monoxide diffusion <

285 70% (n= 4 patients) or obstructive syndrome (n= 4 patients). Bronchoscopy was
286 performed in 19 patients and was with macroscopical abnormal aspect in 2 patients,
287 with a of vascular lakis in one patient and an aspect of endobronchial livedo in
288 another patient. Bronchoalveolar lavage was performed in 8 patients and was found
289 abnormal in 7 of them with hyperlymphocytosis > 15%.

290 *Other medical investigations.* Other medical investigations results were showed in
291 **table 3**. In SLG cohort, cardiac tests performed consisted of electrocardiogram in 15
292 patients, transthoracic echocardiogram in 12 patients and cardiac *magnetic*
293 *resonance imaging* in 4 patients. No patient in SLG cohort was diagnosed or
294 suspected with a cardiac localization of sarcoidosis. Ten patients in SLG cohort had
295 undergone specialized ophthalmological with slit lamp examination of the anterior
296 segment and posterior segment of eye. Ophthalmic abnormalities related to
297 sarcoidosis were found in two patients: one patient had symptomatic bilateral uveitis
298 with a decrease of visual acuity, and asymptomatic choroidal lesions was detected in
299 the other patient.

300 **Sarcoidosis management**

301 *Treatment of sarcoidosis.* The treatment and management of sarcoidosis associated
302 with immunotherapy is summarized in **table 4**. In SLG cohort, 21 (75.0%) patients did
303 not receive specific therapy for sarcoidosis and had received simple monitoring. Five
304 (17.9%) patients were treated with systemic oral corticosteroid, at dose ranging from
305 0.5 to 1 mg/kg per day. Two (7.1%) patients received oral hydroxychloroquine. No
306 patient required immunosuppressive therapy for the management of sarcoidosis. No
307 patient required oxygen therapy supplementation for the management of sarcoidosis.
308 After a median (range) follow-up of 31.6 (6.3 to 60.3) months from sarcoidosis
309 diagnosis radiological improvement of sarcoidosis (spontaneous or with
310 corticosteroids treatment) was reported in 20 (71.4%) patients and stability of

311 radiological sarcoidosis was observed in 8 patients (28.6%). The patient with stage IV
312 Scadding stage with bronchial distortion and fibrosis lung was treated with systemic
313 corticosteroids and the radiological sarcoidosis features partially regress thereafter.

314 *Immunotherapy continuation.* Following sarcoidosis diagnosis, immunotherapy was
315 continued with no interruption in 6 (21.4%) patients, was temporarily hold in 3
316 (10.7%) patients, and permanently discontinued in 19 (67.9%) patients. Of the 19
317 patients who permanently discontinued immunotherapy, discontinuation was related
318 to sarcoidosis (n=12), cancer disease progression (n=3), other immune-related
319 adverse events (n=1) or physician decision (n=3).

320 **Radiologic features and Scadding stages classification of sarcoidosis.**

321 The radiological features of sarcoidosis associated with immunotherapy are detailed
322 in **table 3** and depicted in **figure 2**. Pulmonary CT scans was performed in all
323 patients in SLG cohort and showed bilateral mediastinal-hilar lymphadenopathy
324 (n=26; 92.9%), lung micronodules (n=9; 32.1%), interstitial subpleural curves lines
325 (n=6; 21.4%), pleural granulomatous infiltration (n=5; 17.9%), condensing alveolar
326 opacities (n=3; 10.7%), ground glass opacities (n=2; 7.1%), miliary aspect opacities
327 (n=2; 7.1%), or tracheal-bronchial distortion or fibrosis (n=1; 3.6%). A review of
328 imaging prior to initiation of immunotherapy revealed in 1 patient, CT images of peri-
329 hila lymph nodes reliable with pre-existing granulomatosis. The radiographic
330 Scadding stages for sarcoidosis classification consisted of stage 0 in 2 (7.1%)
331 patients, stage I in 13 (46.4%) patients, stage II in 11 (39.3%) patients, stage III in 1
332 (3.6%) patient; and stage IV in 1 (3.6%) patient.

333 A PET scan was performed in 20 of the 28 patients in SLG cohort (**table 3**). In 20 of
334 20 (100%) patients for whom PET was performed, increased FDG uptake above
335 mediastinal background uptake was found in at least one granulomatous lesion. The

336 median (range) standardized uptake maximal value was 11.0 (4.6 - 22.9). All lymph
337 nodes of sarcoidosis were positive FDG uptake above mediastinal background
338 uptake. The lung interstitial sarcoidosis nodular lesions of size ≥ 10 mm were found
339 FDG avid with positive FDG captation. Pulmonary micronodular lesions < 10 mm did
340 not capture FDG. One patient with skin localization of sarcoidosis had TEP CT
341 performed, showing avid FDG captation on the skin sarcoidosis lesions. One patient
342 with liver sarcoidosis had TEP CT performed and was not positively captured FDG on
343 liver localization of sarcoidosis.

344 **Outcome of patients with overall survival analysis.**

345 *Patients with all tumor types.* In a non-adjusted analysis of patients with all tumor
346 types, the overall survival was longer in the SLG cohort than in the control cohort (OS
347 median not reached versus 35.9 months respectively, HR=0.232 (95%CI: 0.086-
348 0.630; $p=0.002$) (**figure 3**). When adjusted on patient age > 62 vs ≤ 62
349 years, combination immunotherapies versus immunotherapy in monotherapy, and ≥ 1
350 line(s) of anti-cancer treatment received versus first line setting and melanoma
351 versus other tumor types; sarcoidosis remained independently associated with a
352 lower risk of death (HR=0.313; 95%CI: 0.114-0.857; $p=0.024$).

353 *Patients with melanoma.* In a non-adjusted analysis in the subgroup of patients with
354 melanoma, patients with sarcoidosis were at lower risk of death (HR=0.239; 95%CI:
355 0.072 - 0.789; $p=0.010$) (**figure 3**). When adjusted on patient age > 62 versus ≤ 62
356 years, combination immunotherapies versus immunotherapy in monotherapy and ≥ 1
357 line(s) of anti-cancer treatment received versus first line setting; sarcoidosis remains
358 independently associated with lower risk of death (HR=0.289; 95%CI: 0.087-0.960;
359 $p=0.043$).

360 **DISCUSSION**

361 This first case-control study of patients with cancer and sarcoidosis associated with
362 immune checkpoint inhibitors found that sarcoidosis was generally of mild to
363 moderate severity (grade 1-2 in 92.9% of patients) with one in 28 patients (3.6%)
364 presented lung fibrosis features on CT scan. These results are in line with the recent
365 review of Cornejo et al reporting very occasional severe cases of pulmonary fibrosis
366 related to sarcoidosis associated with immunotherapy (13).

367 The outcome of patients with sarcoidosis in our study was favorable, with better
368 overall survival as compared with patients experiencing other immunological
369 toxicities. It is difficult to declare whether this improved survival is linked to the
370 sarcoidosis itself, because several potential biases in analysis can interfere, such as
371 heterogeneous population and biases by the tumor histology type, or immortality bias
372 by sarcoidosis event. Nevertheless, patients with diagnosed sarcoidosis in our
373 experience have an excellent overall survival (median of OS was not reached with
374 median follow-up of 31.6 months) and therefore highlights those patients with
375 sarcoidosis should not be misdiagnosed with tumor progression. One hypothesis to
376 explain the better outcome of patients with SLG is granulomatosis reaction might also
377 translate in optimal immune reaction against the tumor. Our findings indicate that
378 outcome of patients with SLG were consistent with Tetzlaff MT and al. study who
379 reported sarcoidosis related to ICI could be associated with a better outcome of
380 patients (19).

381 From this study, we found that the combination of anti-PD1 plus anti-CTLA4 and
382 melanoma tumor type were more frequently associated with sarcoidosis. Some
383 studies suggested that anti-CTLA4 generated disequilibrium between effector and
384 regulatory T lymphocytes (T reg cells) and may potentially participate in the formation
385 of granuloma in health tissue (20) (21). In our study, whether the development of
386 sarcoidosis was linked to the combination therapy (anti-CTLA4 plus anti-PD1) or to

387 the melanoma cancer makes it difficult to conclude because of the two confounding
388 factors (22) .

389 From our study, we were surprised to not find sarcoidosis in patients treated for lung
390 cancer. A selection bias in our analysis could have been probable, as patients may
391 not have been referred to the ImmunoTOX committee. However, in literature we
392 observed few cases of sarcoidosis associated with immunotherapy in patients with
393 lung cancer, most of sarcoidosis patients were treated for melanoma. In the review
394 by Apalla et al, 6 cases of ICI-induced SLG were observed with lung cancer out of 80
395 cases and including 65 melanomas. One explanation could be that sarcoidosis
396 lesions being mainly thoracic, they could be misdiagnosed with tumor progression
397 and therefore underdiagnosed (9). Another explanation is that melanoma tumor is by
398 itself more of an immunogenic tumor and should be more frequently associated with
399 sarcoidosis reactions. Several studies have suggested potential links between
400 sarcoidosis and certain tumor types of cancers, in particular melanoma and
401 Hodgkin's lymphoma (6,7), even suggesting that sarcoidosis in some patients, could
402 be a paraneoplastic condition. Interestingly, melanoma and Hodgkin were also the
403 most sensitive tumor types to respond to immune checkpoint inhibitors (23).

404 In clinical practice, sarcoidosis in a CT scan, can mimic cancer disease progression,
405 and neither biology nor radiology can differentiate completely between them. The
406 sarcoidosis diagnosis could therefore be based on the advice of an experienced
407 radiologist and in histology confirmation to avoid any misdiagnosis. Sarcoidosis is
408 therefore a diagnostic challenge because a misdiagnosis between sarcoidosis and
409 cancer progression could lead to the premature discontinuation of immunotherapy
410 when it is in fact an effective treatment for cancer.

411 In comparison with data in literature, we did not find any major difference between
412 the clinical presentations of sarcoidosis associated with immunotherapy and

413 idiopathic sarcoidosis. The most frequent localizations of sarcoidosis in our study
414 were the mediastinal-hilar lymph nodes (92.9%) and the lungs (50.0%), like what is
415 found in idiopathic sarcoidosis studies (24). From our study we found few cases of
416 extra-thoracic sarcoidosis, alone (stage 0 Scadding stage was found 7.1% of
417 patients), similarly with results from other studies of idiopathic sarcoidosis (25). In
418 literature, management of SLG associated with immunotherapy required systemic
419 corticosteroid treatment in more than 40% of cases (44% in the study of Teztlaff et
420 al., and 41% in the review of Rambhia et al.) (14,19). In our study, corticosteroids
421 were given in 17.9% of patients. The differences in corticoids management are
422 difficult to interpret given the heterogeneous practices from one center to another and
423 the absence of available guidelines for sarcoidosis associated with immunotherapy.
424 In our study, corticosteroids were infrequently used because few patients were
425 symptomatic, and sarcoidosis was generally considered a non-severe complication in
426 most of cases. Recommendations for the use of corticosteroids in sarcoidosis
427 associated with immunotherapy could be based on idiopathic sarcoidosis
428 recommendations. Thus, systemic corticosteroids should be reserved for patients
429 with symptomatic involvement or at-risk organs such as lung, heart, liver, kidney, eye
430 or central nervous system(26).

431 From a practical point of view in the management of patients, one can question the
432 need to obtain histological documentation in the face of any suspicion of sarcoidosis.
433 Histological confirmation does not seem essential in all cases of sarcoidosis,
434 especially when the radiologist is confident in his diagnosis. However, we believe that
435 at the stage of current knowledge, that in the event of sarcoidosis associated with
436 immunotherapy, this histological confirmation seems important to discuss, especially
437 so as not to confuse it with tumor progression.

438

439 We acknowledge the limitations of our study. The retrospective analysis methodology
440 and the heterogeneity of the patients in SLG and control cohorts represented a
441 limitation in the analysis interpretation. Another limitation was the recruitment of
442 patients by addressing to the immunoTOX committee, that could represent a bias
443 declarative method for the study. However, given the uncommon nature of
444 sarcoidosis, retrospective studies to screen a large number of patients remain the
445 most effective way in identifying enough patients.

446

447 **CONCLUSION**

448 Sarcoidosis associated with immunotherapy were a non-severe immune-related
449 complication and were correlated with improved overall survival. Patients with
450 sarcoidosis associated with immunotherapy demonstrated favorable outcomes and
451 should not be misdiagnosed with tumor progression.

452

453

454

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461 **Author contributions**

462 Study concepts: CC, JMM, SA, JLP, OL

463 Data acquisition : CC, SA, JMM, SH

464 Quality control of data and algorithms: JMM, SA, CP, SH

465 Data analysis and interpretation: CC, SA, JMM, JLP, OL

466 Statistical analysis: CP, CC

467 Manuscript preparation: JMM, SA, CC

468 Manuscript editing: OL, AL, FXD, BB, VTDM

469 Manuscript review: all authors

470

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473 **Conflicts of interest statement.**

474

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482 submitted work.

483 Dr Jean-Marie Michot reports to be of have been in the last 5 years principal/sub-
484 Investigator of Clinical Trials for: Abbvie, Agios, Amgen, Argen-x, Astex,
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487 Pharmamar, Roche, Sanofi, Seattle Genetics, Takeda, Xencor.

488 All other authors have no conflicts of interest to declare.

489

490

491 **Figure legends.**

492 **Figure 1.** Flow chart of the study.

493 **Figure 2.** Radiological features of sarcoidosis lesions associated with
494 immunotherapies. Computed tomography images exposed in the figure were
495 representative of the different sarcoidosis features of patients included in the sarcoid-
496 like granulomatosis cohort.

497 **Figure 3.** Overall survival of patients with sarcoidosis associated with
498 immunotherapy. Overall survival of patients with sarcoidosis associated with
499 immunotherapy treated for all types of tumors (left panel). Overall survival of patients
500 with sarcoidosis associated with immunotherapy treated for melanoma (right panel).

501

502 **Table 1.** General clinical characteristics of the patients included in the sarcoid-like granulomatosis
503 cohort and in the control cohort. Patients included in the sarcoid-like granulomatosis cohort were
504 patients with sarcoidosis confirmed by histology. Patients included in the control cohort were patients
505 with immunological toxicities other than sarcoidosis.
506

	Control cohort n=406	Sarcoid-like granulomatosis cohort n=28	<i>P value</i>
Demographic characteristics			
Sex			
Women	173 (42.6%)	14 (50.0%)	0.445
Men	233 (57.4%)	14 (50.0%)	
Age (range) at the time of immunological toxicity, median in years.	63.1 (19.2-89.6)	56.5 (28.7-75.3)	0.052
Autoimmune history in past medical history (before immunological toxicity)			
Yes	20 (4.9%)	4 (14.3%)	0.061
No	383 (94.3%)	24 (85.7%)	
Characteristics of cancer			
Type of cancer			
Lung or thoracic cancer	125 (30.8%)	0 (-)	<0.001
Skin cancers, all types	94 (23.2%)	21 (75.0%)	<0.001
Melanoma	89 (21.9%)	21 (75.0%)	<0.001
Digestive	35 (8.6%)	0 (-)	0.152
Gynecological or breast	28 (6.9%)	2 (7.1%)	1.000
Head and neck	38 (9.4%)	1 (3.6%)	0.496
Urothelial, kidney or prostate	63 (15.5%)	4 (14.3%)	1.000
Other types	22 (5.4%)	0 (-)	0.384
Immunotherapy regimen			
Anti-PD1 monotherapy	218 (53.7%)	12 (42.9%)	0.329
Anti-PD-L1 monotherapy	31 (7.6%)	0 (-)	0.247
Anti-CTLA4 monotherapy	9 (2.2%)	1 (3.6%)	0.490
Anti-PD1 plus anti-CTLA4 combination	51 (12.6%)	13 (46.4%)	0.002
Other immunotherapy regimen	97 (23.9%)	2 (7.1%)	0.059
Previous exposure to immunotherapy			
Yes	45 (11.1%)	5 (17.9%)	0.351
No	361 (88.9%)	23 (82.1%)	
Previous exposure to targeted anticancer therapy			

Yes	104 (25.6%)	7 (25.0%)	1.000
No	302 (74.4%)	21 (75.0%)	
Median (range) of previous line(s) of systemic anticancer therapy	1 (0-12)	0 (0-3)	<0.001
Immune-related adverse events (other than sarcoidosis)			
Severity (CTCAE)			
Grades 1-2	160 (39.4%)	8 (28.6%)	<0.001
Grades 3-4	233 (57.4%)	2 (7.1%)	
Grade 5*	13 (3.2%)	0 (-)	
Distribution of immune-related adverse events			
Mucocutaneous	28 (6.9%)	2 (7.1%)	NT
Digestive	54 (13.3%)	1 (3.6%)	
Endocrine	25 (6.2%)	3 (10.7%)	
Lung	78 (19.2%)	1 (3.6%)	
Neurological or neuromuscular	35 (8.6%)	1 (3.6%)	
Hepatic	45 (11.1%)	1 (3.6%)	
Other immune-related adverse events	141 (34.7%)	1 (3.6%)	

507 NT : not tested
508 * the 13 death causes in control group were; pneumonitis (n = 3), hyperprogression (n = 2), auto-immune hemolytic anemia (n =
509 1), immune-related aplastic anemia (n = 1), capillary leak syndrome (n = 1), cytokine release syndrome (n = 1), hepatitis (n = 1),
510 myocarditis (n = 1), myositis with mitochondrial cytopathy (n = 1), myositis with diaphragmatic palsy (n = 1).
511 PD1 : programmed cell death 1
512 PD-L1 : programmed cell death ligand 1
513 CTLA4 : Cytotoxic-T-Lymphocyte- Antigen 4 protein
514 CTCAE : Common Terminology Criteria for Adverse Events

515

516 **Table 2:** Clinical characteristics of patients with sarcoidosis associated with immunotherapy and their
517 sarcoidosis features (patients included in the sarcoid-like granulomatosis cohort).
518

		Number of patients or value of examination (n= 28)	%
Patient demographics characteristics	Men	14	50.0
	Women	14	50.0
	Age at diagnosis of sarcoidosis, median in years (range)	56.5 (28.7-75.3)	-
	Ethnicity		
	Caucasian	21	75.0
	African or Caribbean	0	-
	Other	0	-
	Unknow	7	25.0
	Disease setting for immunotherapies.		
	Metastatic	22	78.6
Adjuvant	5	17.9	
Neoadjuvant	1	3.6	
Anticancer immunotherapy characteristics and results	Number of immunotherapy cycles before sarcoidosis diagnostic, median (range)*	5.5 (1-40)	-
	Time from immunotherapy start to sarcoidosis diagnosis, median in months (range)*	5.1 (1.5-31.5)	-
	Best antitumor response obtained with immunotherapy		
	Partial response	13	46.4
	Complete response	4	14.3
	Stable disease	4	14.3
	Progressive disease	1	3.6
	NA (adjuvant or neoadjuvant treatment)	6	21.4
Granulomatosis features	Granulomatous localizations** per patient, median number (range)	2 (1-4)	-
	Granulomatosis localizations in all patients		
	Mediastinal lymph nodes	26	92.9
	Lung infiltrate	14	50.0
	Skin	3	10.7
	Kidney	2	7.1
	Liver	2	7.1
	Eye	2	7.1

Symptoms of sarcoidosis	Extra-thoracic lymph nodes	2	7.1
	Heart	0	-
	Clinical symptoms		
	Yes	15	53.6
	No (asymptomatic)	13	46.4
	Symptoms		
	Cough	5	17.8
	Dyspnea	8	28.6
	Mucocutaneous	3	10.7
	Ocular	1	3.6
	Severity of sarcoidosis according to CTCAE		
Grade 1-2	26	92.9	
Grade 3-4	2	7.1	

519 * date of sarcoidosis diagnosis was date of biopsy showing granulomatosis lesions.

520 ** the number of granulomatosis localizations was calculated according to the World Association of Sarcoidosis
521 and other Granulomatous Disorders classification

522 CTCAE: Common Terminology Criteria for Adverse Events

523

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525

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Table 3: Laboratory, radiological features and other medical investigations performed to assess sarcoidosis associated with immunotherapy (patients included in the sarcoid-like granulomatosis cohort).

	Number of patients or value of examination, n= 28 patients.	%
Laboratory values at sarcoidosis diagnosis		
Calcemia in mmol/L, median (range) [normal values: 2.20 - 2.65 mmol/L]	2.39 (2.11 - 2.56)	
CRP in mg/L, median (range) [normal values: < 5 mg/L]	2.35 (0.4 - 52.6)	
Angiotensin converting enzyme, median (range) [normal values: < 70 UI/L]	50.5 (25 - 88)	
Creatinine, median (range) [normal values: 49 - 90 µmol/L]	79 (46 - 167)	-
Gammaglobulinemia, median (range) [normal values: 7,3 - 13,9 g/L]	10.8 (6.4 - 22.1)	
AST (median, range) [normal values: < 35 UI/L]	25 (7 - 247)	
ALT (median, range) [normal values: < 35 UI/L]	23 (8 - 403)	
Radiological features of sarcoidosis		
Delay between immunotherapy first cycle and first CT scan abnormalities of sarcoidosis, median in months (range)	2.8 (1.0-29.3)	-
Parenchyma lung sarcoidosis involvement on CT scan		
Yes	14	50.0
No	14	50.0
Thoracic radiological abnormalities features of sarcoidosis on CT scan.		
Mediastinal lymph nodes	26	92.9
Lung micronodules	9	32.1
Interstitial subpleural curves lines	6	21.4
Pleural granulomatous infiltration	5	17.9
Condensing alveolar opacities	3	10.7
Ground glass opacities	2	7.1
Miliary opacities	2	7.1
Tracheal or bronchial distortion	1	3.6
Lung fibrosis	1	3.6
Scadding stage on CT scan.		
Stage 0	2	7.1
Stage I	13	46.4
Stage II	11	39.3
Stage III	1	3.6
Stage IV	1	3.6
FDG-PET avidity of sarcoidosis lesions.		
Performed	20	71.4
Yes	20	71.4
No	0	-

SUV max on FDG-PET, of sarcoidosis lesions; median (range)	11 (4.6-22.9)	-
Complementary medical investigations for sarcoidosis and their results		
Bronchoscopy		
Performed	19	67.9
Normal	17	60.7
Abnormal	2	7.1
Bronchoalveolar fluid		
Performed	8	28.6
Normal	1	3.6
Abnormal*	7	25.0
Respiratory functional tests		
Performed	19	67.9
Normal	11	39.3
Abnormal**	8	28.6
ECG		
Performed	15	53.6
Normal	14	50.0
Abnormal	1	3.6
Ultrasounds cardiac		
Performed	12	42.9
Normal	10	35.7
Abnormal	2	7.1
Cardiac MRI		
Performed	4	25.0
Normal	4	25.0
Abnormal	0	-
Ophthalmological examination		
Performed	10	35.7
Normal	8	28.6
Abnormal	2	7.1

530 *7 patients had hyperlymphocytosis > 15% on bronchoalveolar lavage results.

531 **4 patients had an obstructive syndrome, and 4 other patients had a decreased DLCO < 70%

532 ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; CT: computerized tomography;

533 ECG: electrocardiogram; FDG-PET: Fluorodeoxyglucose positron emission tomography; MRI: *magnetic resonance imaging*;

534 SLG: sarcoid-like granulomatosis; SUV: Standardized uptake value

535

536 **Table 4:** Outcomes and management of patients with sarcoidosis associated with
537 immunotherapy (patients included in the sarcoid-like granulomatosis cohort).

	n	%
--	---	---

Systemic treatment for sarcoidosis		
Yes	7	25.0
Systemic corticoids	5	17.9
Immunosuppressants or immunomodulators	0	-
Other therapy*	2	7.1
No	21	75.0
Management of immunotherapy after sarcoidosis		
Temporary hold and resumed	3	10.7
Permanently discontinued	19	67.9
Continued without interruption	6	21.4
Sarcoidosis outcome on control CT scan		
Sarcoidosis features improvement	20	71.4
Sarcoidosis stability	8	28.6
Sarcoidosis worsening	0	-
Cancer outcome on control CT scan		
Tumour progression	11	39.3
No tumor progression	17	60.7

538 * other therapies in 2 patients were hydroxychloroquine orally given.

539 CT: computerized tomography

540

541

542

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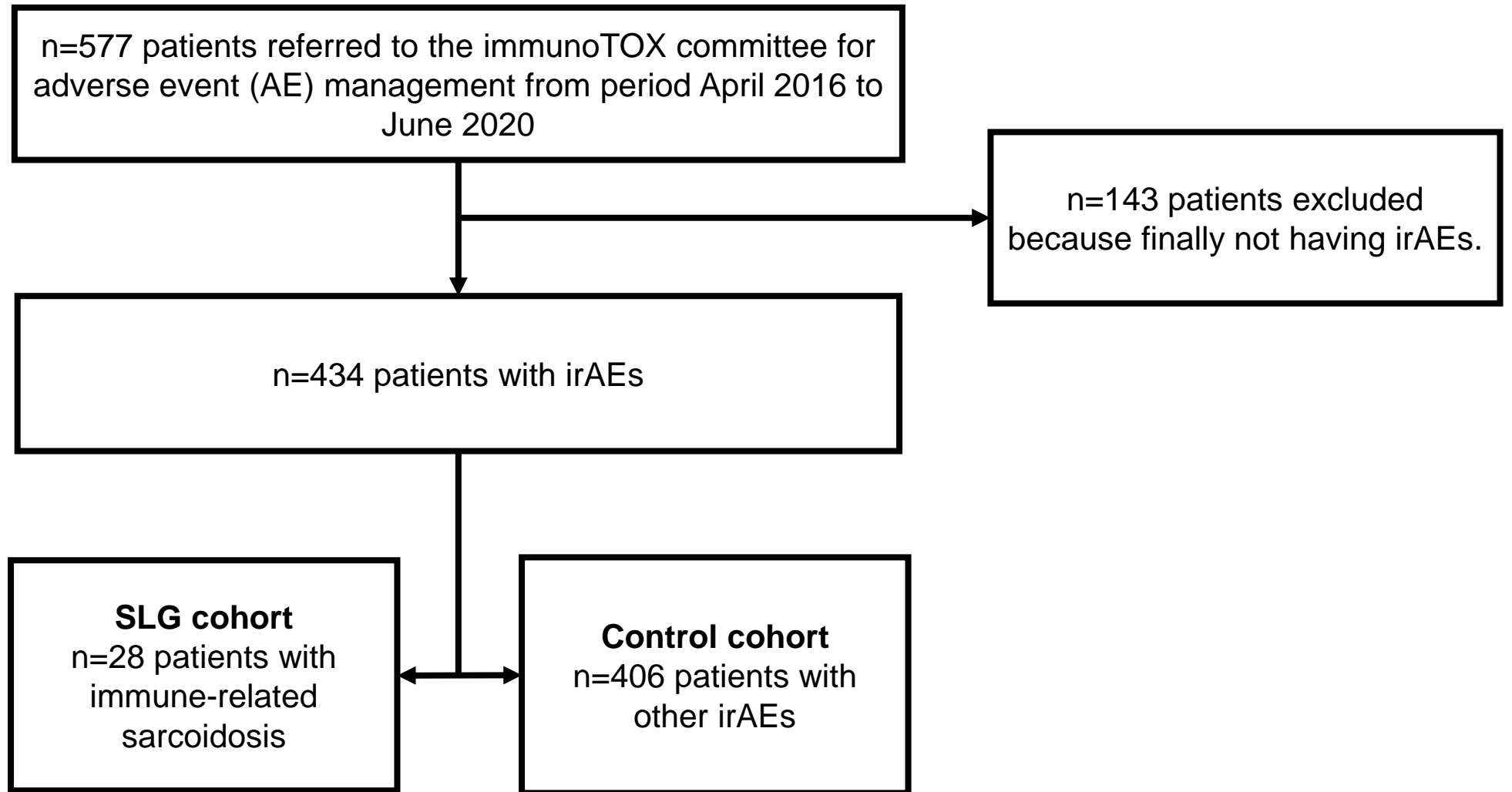
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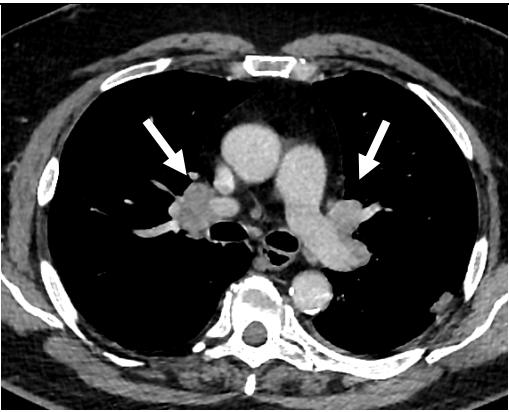
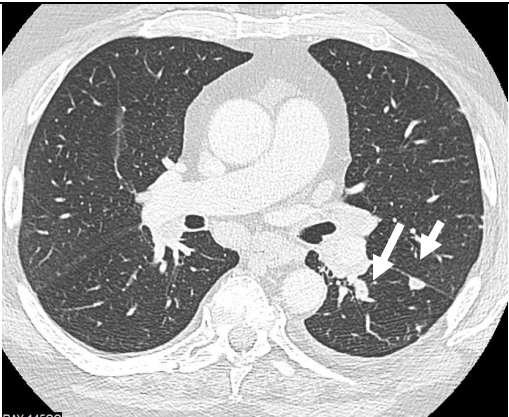
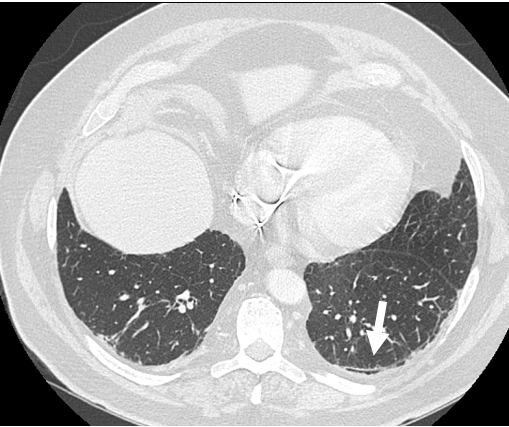
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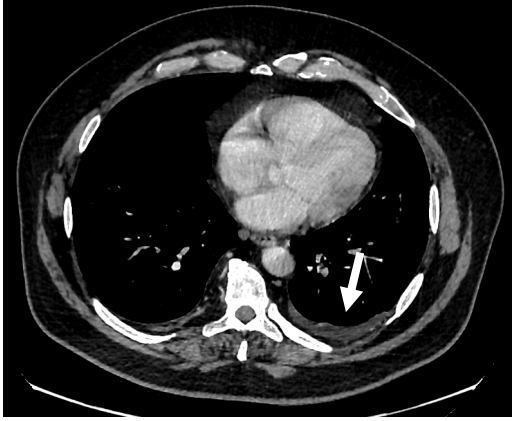
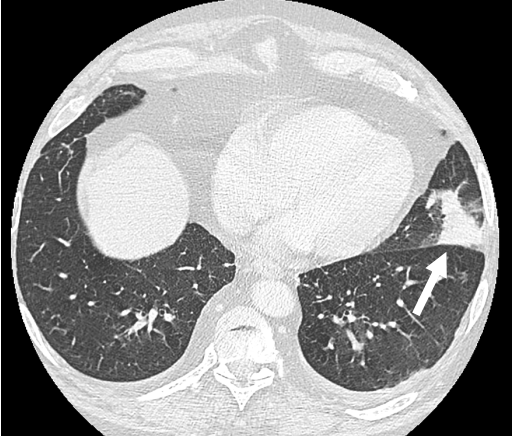
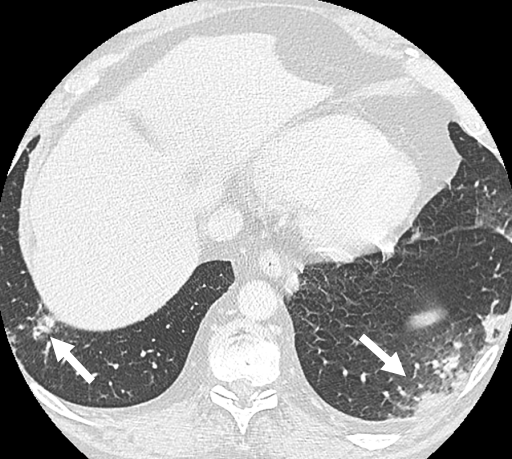
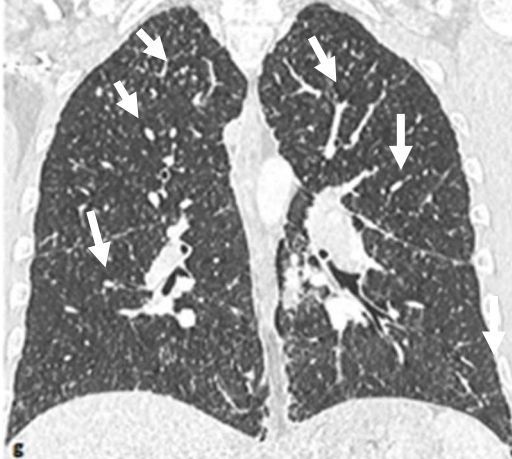
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Figure 1: flow-chart of the study.

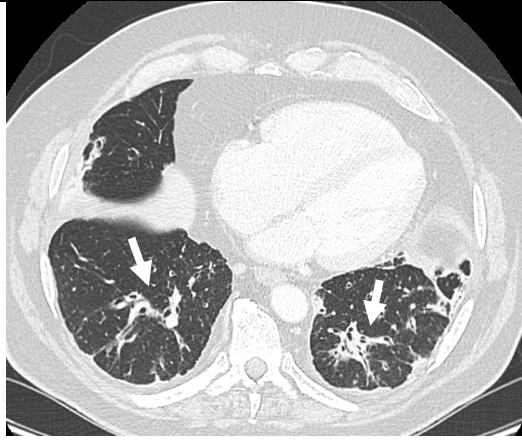


Radiological features of sarcoidosis associated with immunotherapy. Number of patients (%)	Representative image and description on CT scan	
Mediastinal lymph nodes n=26 (92.9%)		Mediastinal lymph nodes, non-compressive, non-associated with necrosis.
Lung parenchyma micronodules n=9 (32.1%)		Lung parenchyma micronodules, less than 1 cm, distributed in subpleural or peri-scissural area.
Interstitial subpleural curves lines n=6 (21.4%)		Lung interstitial opacities, with curved lines distributed in subpleural areas

<p>Pleural granulomatous infiltration</p> <p>n=5 (17.9%)</p>		<p>Low abundance pleural effusion usually unilateral, with regular thickened pleural effusion in contact.</p>
<p>Condensing alveolar opacities</p> <p>n=3 (10.7%)</p>		<p>Localized condensing alveolar opacities.</p>
<p>Ground glass opacities.</p> <p>n=2 (7.1%)</p>		<p>Ground glass opacities predominantly at the lung bases</p>
<p>Miliary aspect opacities</p> <p>n=2 (7.1%)</p>		<p>Bilateral diffuse interstitial alveolar opacities with a miliary appearance.</p>

**Tracheal bronchial distortion
or fibrosis**

n=1 (3.6%)



Bronchiectasis, tracheal distortions, or peri bronchial thickening with bronchial distortions.

Figure 2: Overall survival in patients with sarcoidosis associated with immunotherapy.

Overall survival in patients with all tumor types.

Overall survival in patients with melanoma.

