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Cancers synchrones et sclérodermie : Notre expérience en Médecine Interne

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Propos

- La découverte concomitante (≤ 06 mois ou à ≥ à 12 mois) dans l'année d'une sclérodermie systémique 'ScS' et d'un cancer viscéral = cancer synchrone.

C. G. Joseph et al. Association of the autoimmune disease scleroderma with an immunologic response to cancer. Science 2014; 343:152-7

C. Masson, M. Lecouffe-Desprets, A. Néel, A. Achille, C. Durant, M. Hamidou, C. Agard. Vol 38 - N° S1, P. A168 - juin 2017

Stojan G, Illei PB, Yung RC, Gelber AC. Raynaud's phenomenon, inflammatory arthritis, and weight loss: pay attention to the man behind the curtain. Arthritis Care Res (Hoboken) 2014;66:1263–8.

Claude Bachmeyer MD, Christopher Rein MD: Anti–RNA Polymerase III Autoantibody–Positive Scleroderma as a Paraneoplastic . Syndrome: Comment on the Article by Stojan et al

Buts

- Rapporter notre expérience en médecine Interne.
  - Profil de nos malades comparativement aux données de la littérature
  - Signes prédictifs +/- et pronostic de survenue d'un cancer au cours de la ScS : Ac anti-ARN pol III
  - Lien cancers et auto-immunité

Stojan G, Illei PB, Yung RC, Gelber AC. Raynaud's phenomenon, inflammatory arthritis, and weight loss: pay attention to the man behind the curtain. Arthritis Care Res (Hoboken) 2014;66:1263–8.
Racanelli V, Prete M, Minoia C, Favoino E, Perosa F. Rheumatic disorders as paraneoplastic syndromes. Autoimmun Rev 2008;7:352–8.
Moinzadeh P, Fonseca C, Hellmich M, Shah AA, Chighizola C, Denton CP, et al. Association of anti–RNA polymerase III autoantibodies and cancer in scleroderma. Arthritis Res Ther 2014;16

Brown J.M., Pfau J.C., Perhouse M.A., et al. Silica, apoptosis and autoimmunity *J Immunotoxicol* 2005 ; 1 : 177-187

Patients et Méthodes

- Etude de dossiers de consultations et d'hospitalisation colligés de Janvier 2014 à Janvier 2017.

- Séjour en médecine interne

- Recrutement : médecine interne, pneumologie, oncologie.

Protocole de travail

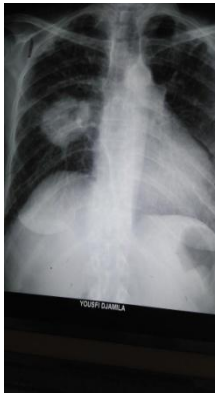
- Ont été inclus les patients avec :
  - ScS : sclérodermie avérée répondant aux critères 2013.
  - Cancer : certitude anatomopathologique.
  - La survenue du cancer dans l'année du diagnostic de la ScS.
  - Un suivi minimal d'une année.

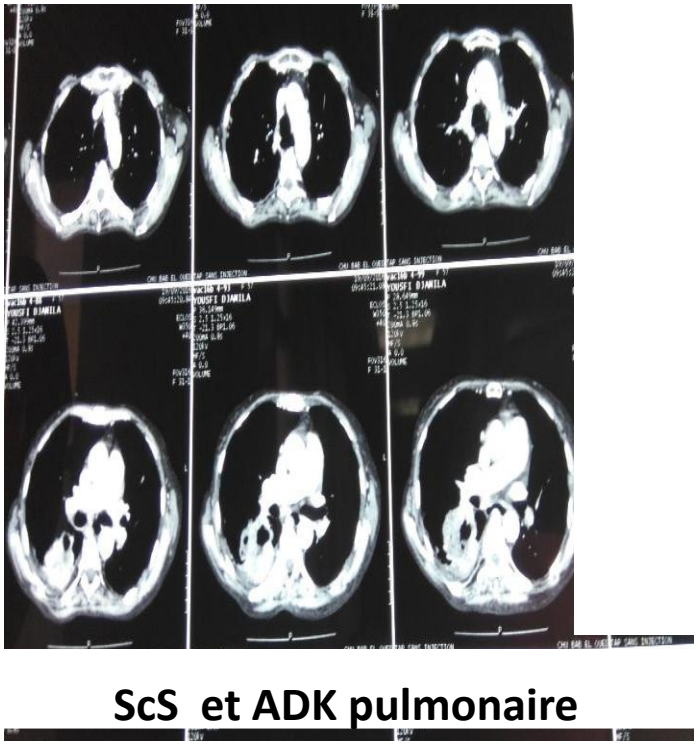
Résultats

- Sur 44 cas de ScS répartis en 39 femmes et 5 hommes
- Age moyen de 49 ans [21-55]
- Nombre de cancers synchrones : 5 (4 Femmes et un homme)
- Notion de cancer familial : 1 (F)

Type de Cancers et ScS

- Adénocarcinome pulmonaire sur lésions pulmonaires fibrosantes (2)
- Thymosarcome (1H)
- Cancer infiltrant du sein (2).





ScS et ADK pulmonaire

Scs et Cancers : clinique

- La survenue d'un cancer était associée à une détérioration des fonctions cardio-respiratoires (3).
- A l'extension de la sclérose cutanée (3)
- A l'aggravation des ulcères digitaux (2).
- A la survenue d'une altération de l'état général (3).
- A la survenue d'un prurit féroce sans cholestase hépatique (2).

Facteurs oncogènes associés

- Tabac : 1
- Exposition la silice : 0
- Exposition aux solvants : 1
- Immunosuppresseurs, biothérapie : 0
- PID : 4/5

Circonstances de découverte

- Suivi d'une Scs : 2
- Bilan initial d'une Scs : 1
- Concomitante : 2 (manifestations systémiques d'un cancer)

Racanelli V, Prete M, Minoia C, Favoino E, Perosa F. Rheumatic disorders as paraneoplastic syndromes. Autoimmun Rev 2008;7:352–8.

Caractéristiques Immuno-cliniques

	Patient 1 F 54 ans	Patient 2 F 51 ans	Patient 3 F : 55 ans	Patient 4 F 21 ans	Patient 5 H 55 ans
KC	POUMON	SEIN	POUMON	SEIN	THYMUS
SG	NON	NON	NON	NON	AEG
SCLÉROSE CUTANÉE	**DIFFUSE**	LIMITÉE	LIMITEE	**DIFFUSE**	**DIFFUSE**
UD	OUI	NON	OUI	NON	OUI
POUMON	PID	OUI	OUI	NON	OUI
CŒUR	NON	NON	NON	NON	CORONARIEN
REIN	NON	NON	NON	NON	OUI
TD	RGO	ECTASIES VASCUL	POC	RGO	OUI
AUTRES	SD SEC	THYROÏDITE AI	THYROIDITE	SD SEC	TABAC ++ AVCI
IMMUNOLOGIE					
•AAN	1/640	1/1000	1/640	1./1000	1/640
•ANTI-TOPOISOMÉRASES	OUI	NON	NON	OUI	OUI
•ANTICENTROMERES	NON	NON	OUI	NON	NON
•ANTIRNA POLY MERASE III	NON	NON	NON	OUI	OUI
•ANTI - PM./SCL+	NON	NON	OUI	NON	NON
SURVIE	**10 MOIS**	EN VIE	**07 MOIS**	EN VIE KC SEIN FAM	**04 MOIS**

Evolution

- Le cancer était à l'origine du décès dans un délai court (3) en dépit d'un protocole intensif, d'une exérèse chirurgicale (4) et d'une anesthésie - réanimation adaptée (2).

Data from the EUSTAR database			
	Anti-RNAP+ (n=223)	Anti-RNAP- (n=4,763)	*p*-value
Male gender	24.7%	14.4%	<0.0001
Diffuse cutaneous involvement	55.3%	28.2%	<0.0001
Fibrosis at chest x-ray	42.3%	31.3%	0.008
Renal crisis	10.7%	1.3%	<0.0001
Joint contractures	45.1%	30.0%	<0.0001
Data from the case-control study			
	Anti-RNAP+ (n=126)	Anti-RNAP- (n=137)	*p*-value
Malignancy	18.2%	8.0%	0.02
Malignancy synchronous with the onset of SSc	5.6%	0.7%	0.03
GAVE	8.7%	0.7%	0.01

Figure 1. Clinical significant associations of patients with anti-RNA polymerase positivity

Discussion

- **Association Ac anti-ARN pol III et néoplasie** : confirmé **(18% vs 8%),** néoplasies synchrones (M-6 à M+12) du diagnostic de ScS (5,6% vs 0,7%). ***Lazarroni MG et a****l*

- **Association significative entre anti-PM/Scl 100 et néoplasie**, 1/3 des cas dans les 36 mois suivant du Dc de ScS, ADK mammaire cancer pulmonaire ou hémopathie. ***Bruni C et al***

- **Cancer et Sclérodermie : Lien ?**
  - cellules néoplasiques seraient caractérisées par la mutation du gène de l'auto-antigène ARN Pol III.
  - l'expression par la tumeur de l'auto-antigène muté induirait une réaction cellulaire LT CD4+ et LT CD8+, puis secondairement humorale (LB), avec la production d'Ac anti ARN Pol III qui seraient à l'origine de la sclérodermie.

Phénomène d'auto-immunité induite par un auto-antigène tumoral génétiquement modifié

- C. G. Joseph et al. Association of the autoimmune disease scleroderma with an immunologicresponse to cancer. Science 2014; 343:152-7
- C. Masson, M. Lecouffe-Desprets, A. Néel, A. Achille, C. Durant, M. Hamidou, C. Agard. Vol 38 - N° S1, P. A168 - juin 2017
- **T. Martin, Strasbourg, Mars 2014 : Des avancées dans la compréhension des cancers associés aux Sclérodermies .** *Rencontres en Immunologie et Immunothérapie Pratiques (RIIP*

Méta-analyse

Systemic sclerosis (scleroderma) and cancer risk : systematic review and meta-analysis of observational studies.

Bonifazi M, Tramacere, Pomponio G, Gabrielli B, Avvedimento EV, La Vecchia C, Negri E, Gabrielli A.

- **OBJECTIVES :** A higher incidence of cancer in scleroderma patients compared with the general population has been suggested by several observational studies, reporting, however, different estimates. Therefore, we aimed to perform a systematic review and meta-analysis to definitely assess this association.

- **METHODS :** We searched **MEDLINE and Embase for all original articles of observational studies on cancer incidence in scleroderma patients without language restriction published up to December 2011**. Two independent authors reviewed all titles/abstracts and retrieved detailed full-text of potentially relevant articles to identify studies according to predefined selection criteria. Summary estimates were derived using random-effects model and reported as relative risk (RR). Publication bias was evaluated by trim and fill analysis.

- **RESULTS :** From articles initially identified, 16 original studies, involving more than 7000 patients, were included in the present review. Compared with the general population, the summary **RR to develop all invasive cancers in scleroderma patients was 1.75 (95% CI 1.41, 2.18).** The results for selected cancer sites indicated a **strong association with lung cancer (RR 4.35; 95% CI 2.08, 9.09),** and a **significant increased risk also for haematological neoplasms (RR 2.24; 95% CI 1.53, 3.29).** The relation **with breast cancer, suggested in some previous epidemiological studies, was not confirmed (RR 1.05; 95% CI 0.86, 1.29).**

- **CONCLUSION : The present meta-analysis, the first on scleroderma and cancer risk, provides definite estimates on the association**

Perspectives

- Lien pathogénique cancers et sclérodermie/auto-immunité
- Intérêt d'un registre sclérodermie et cancers : Oui
- Identifier des facteurs prédictifs : immunologie peut identifier un groupe à risque les porteurs des anticorps anti-ARN polymérase 3 ou d'anti-Pm-Scl, patients sous immunosuppresseurs, exposés aux solvants, silice et tabac…… aux solvants….

Otsuki T., Maeda M., Murakami S., et al. Immunological effects of silica and asbestos *Cell Mol Immunol* 2007 ; 4 : 261-268
Brown J.M., Pfau J.C., Perhouse M.A., et al. Silica, apoptosis and autoimmunity *J Immunotoxicol* 2005 ; 1 : 177-187
Zaghi G, Koga F, Nisihara RM, Skare TL, Handar A, Utiyama SR, Silva MB. Autoantibodies in silicosis patients and in silica-exposed individuals. Rheumatol Int. 2010;30(8):1071-5
Klein AK, Christopher JP. Evaluation of crystalline silica as a threshold carcinogen. Scandinavian Journal of Work, Environment and Health 1995; 21(SUPPL. 2):95-9
Pairon JC, Brochard P, Jaurand MC, Bignon J. Silica and lung cancer: a controversial issue. Eur Respir J 1991; 4:730-744.
Pairon JC, Legrand-Cattan K. Exposure to silica is involved in the genesis of bronchopulmonary cancer. Revue du Praticien - Medecine Generale 1999; 13(458):781-785

- Identifier des facteurs pronostic
- Algorithme de dépistage des cancers synchrones : intérêts ?

Table 1. Levels of agreement among 82 EUSTAR experts

Degree of agreement with the some statements about a screening for synchronous cancer in SSc anti-RNA Polymerase III positive patients (1-10; 10: fully agree)

Statement	Mean	SD
A screening for synchronous malignancies is recommended	8.73	1.70
A screening for synchronous breast cancer in female patients is recommended with the execution of mammography (or US/MRI when needed)	9.02	1.35
Screening for other malignancies should be guided by clinical suspicion and patient age. Non invasive tests (e.g. fecal occult blood, gynecological evaluation, prostatic specific antigen) may be considered in all patients	8.63	1.48
Serum tumoral markers are NOT useful for screening in every patients	8.59	2.18
A period of 2-5 years of tight surveillance for cancer is recommended	8.26	2.01
If the screening tests for cancer performed at the diagnosis of scleroderma are negative, tests for breast cancers should be repeated (e.g. annually); other tests should be repeated in case of clinical suspicion	7.90	2.14
PET/CT may be considered when aspecific systemic signs suggest the possible presence of neoplasms	8.00	2.02
Further tight surveillance for cancer is not recommended after a period of 2-5 years	7.10	2.27
Prospective studies are needed to clarify how long should the tight surveillance lasts and which exams are most indicated for a screening of cancer in these patients	9.56	1.04

Conclusion

- L'association cancer et ScS, décrite comme non fortuite, mérite d'être évaluée à plus grande échelle .

- Le sur-risque du cancer du poumon serait lié, du moins en partie, aux lésions fibrosantes pulmonaires préexistantes, aux désordres auto-immuns ou à des facteurs communs impliqués dans le cancer et la fibrose pulmonaire comme, dans le syndrome d'Erasmus.

Joseph CG, Darrah E, Shah AA, Skora AD, Casciola-Rosen LA, Wigley FM, et al. Association of the autoimmune disease scleroderma with an immunologic response to cancer. Science 2014;343:152–7

Rosenthal AK, McLaughlin JK, Gridley G, Nyrén O. **I.ncidence of cancer among patients with systemic sclerosis;** . Cancer. 1995 Sep 1;76(5):910-4.

Westerholm P., Ahlmark A., Massing R., et al. Silicosis and risk of lung cancer or lung tuberculosis: a cohort study*Environ Res* 1986 ; 41 : 339-350

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