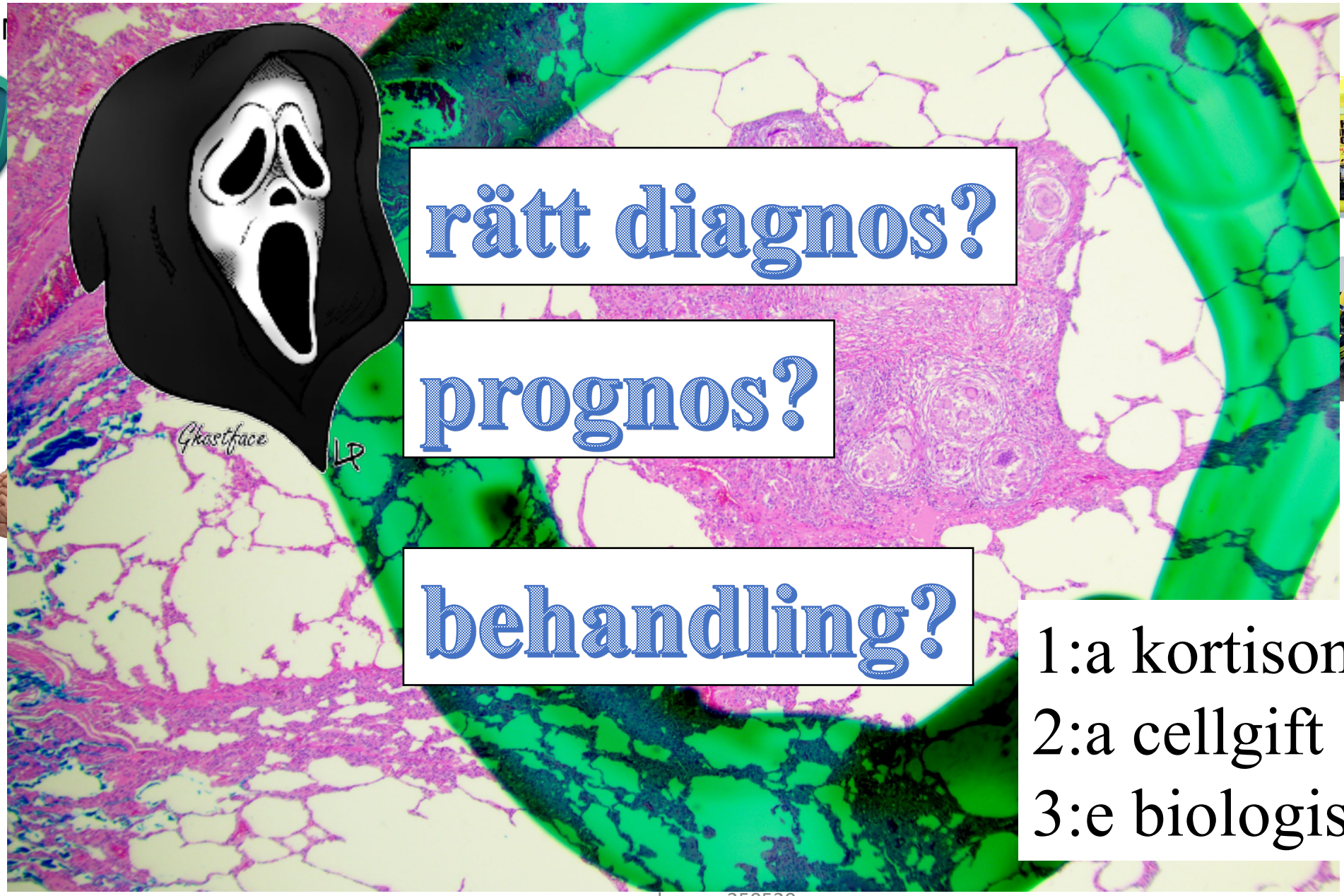
Repetition, datainsamling och en gåta

Susanna Kullberg, docent, överläkare
ME Lung- och allergisjukdomar, Avd för immunologi och lungmedicin, CMM
Karolinska Universitetssjukhuset, Karolinska Institutet

Repetition

GE



rätt diagnos?

prognos?

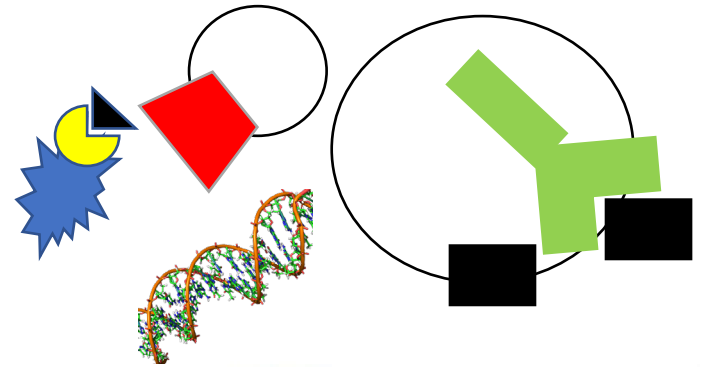
behandling?

1:a kortison
2:a cellgift
3:e biologiska

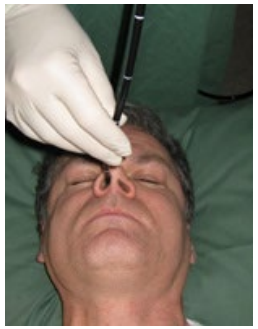
Datainsamling

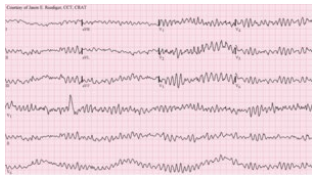
KLINISK ANALYS

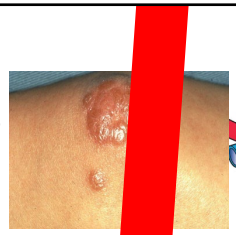
FORSKNINGSANALYS

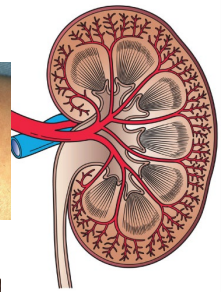


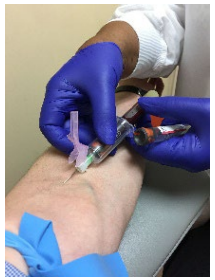
Biomarkörer for diagnos, prognos, behandlingsutfall

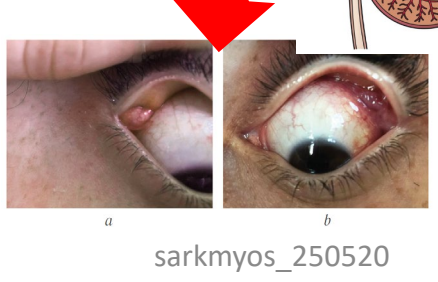






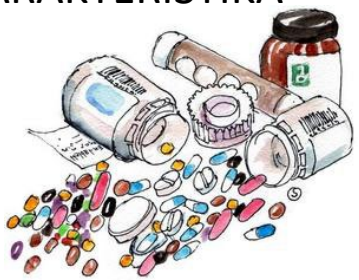




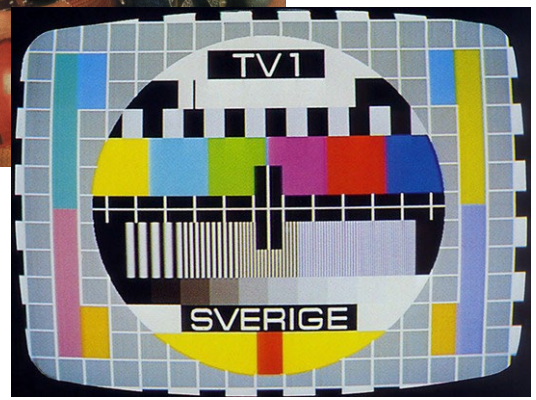


a b

PATIENTKARAKTERISTIKA

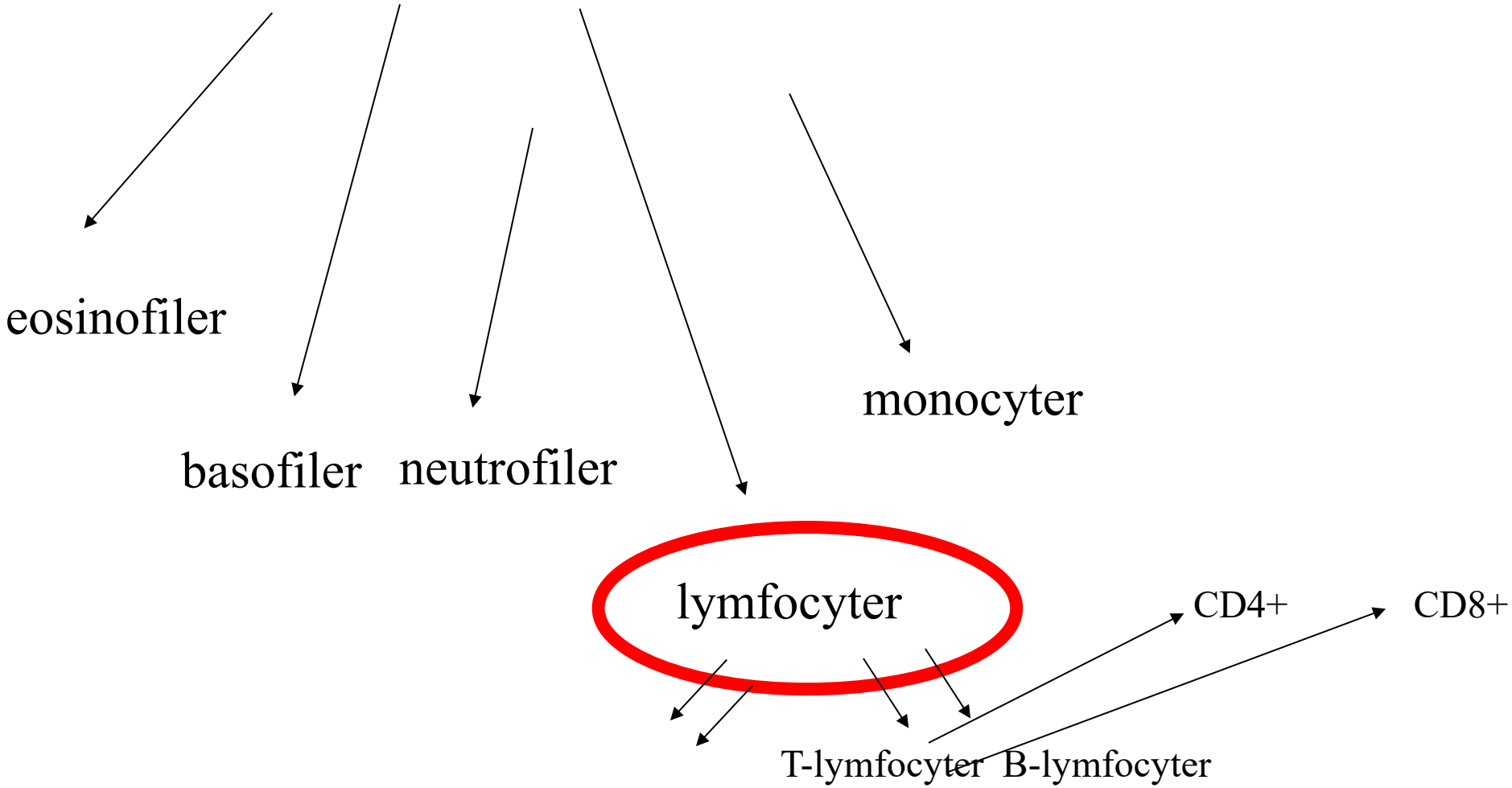


LYMFOPENI



KRONISK SARKOIDOS

VITA BLODKROPPAR



LYMFOPENI

LYMFOCYTOS

Clinical and Experimental Immunology, 2023, **213**, 357–362
https://doi.org/10.1093/cei/uxad052
Advance access publication 10 May 2023
Research Article

Research Article

Peripheral blood lymphopenia in sarcoidosis ass with *HLA-DRB1* alleles but not with lung immur organ involvement

Pernilla Darlington[1,2], Jonas Melin[1], Natalia Rivera[3], Johan Grunewald[3,4], Anders Susanna Kullberg[3,4,*]

[1]Department of Internal Medicine, Södersjukhuset, Sweden
[2]Department of Clinical Science and Education, Södersjukhuset and Karolinska Institutet, Stockholm, Sweden
[3]Respiratory Medicine Division, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
[4]Department of Respiratory Medicine, Theme Inflammation and Ageing, Karolinska University Hospital, Stockholm

*Corresponding author: Susanna Kullberg, Respiratory Medicine Division, Department of Medicine, Karolinska Institutet, Stockh kullberg@ki.se

Abstract

Different human leukocyte antigen (HLA) alleles associate with disease phenotypes in sarcoidosis. Peripheral blo ported as more common in sarcoidosis patients with worse prognosis. The mechanisms behind are unrecognized lymphocytes migrating to lung and/or extra pulmonary organs has been suggested. Insights into associations bet mune cells, clinical phenotype including extra pulmonary manifestations (EPM), and PB lymphopenia may provide m adequate intervention in this patient group. In this study,141 treatment naïve, newly diagnosed patients were re Swedish cohort of sarcoidosis patients. Data on *HLA-DRB1* alleles, lung immune cells from bronchoalveolar lavage fl and clinical parameters including treatment and disease course (chronic vs. resolving) were collected. The patients w lymphopenia associated with male sex, development of non-resolving disease, a need for first- and second-line sys treatment and *HLA- DRB1*07*. No correlation between BALF and PB lymphocytes, and no difference in EPM was with and without PB lymphopenia. In conclusion, PB lymphopenia is associated with a more severe disease phenoty *DRB1*07* allele. The results do not lend support to the hypothesis about sarcoidosis PB lymphopenia being due to a n to other organs. Rather, they provide a basis for future studies on the connection between *HLA-DRB1*07* and PB ly

Keywords: sarcoidosis, lymphopenia, bronchoalveolar lavage

Abbreviations: BALF: bronchoalveolar lavage fluid; HLA: human leukocyte antigen; LS: Löfgren´s syndrome; non-LS: non-Löfgr blood; EPM: extra pulmonary manifestations; TRAV2.3: CD4+ T-cell receptor segment Vα2.3; WASOG: World Association of Sarcoi Disorders.

Background

The clinical presentation of the inflammatory systemic disease sarcoidosis is variable. Virtually any organ can be affected, but the lungs and/or intrathoracic lymph nodes are engaged in most cases. Patients with Löfgren´s syndrome (LS) experience an acute and often self-limiting disease, while patients with non-Löfgren´s syndrome (non-LS) more often present with a slower developing and non-resolving disease. There is no cure and despite treatment with first- and second-line therapy (usually corticosteroids and methotrexate), many pa-

in the lungs, are involved [1]. As op olitis in the lungs, peripheral blood reported already in the 70s in a subs [2, 3].

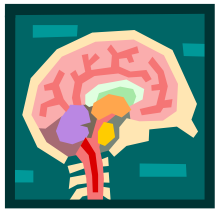
Especially, the human leukocyte an also HLA Class I and Class III gene non-HLA genes have been associate phenotype. Some of these genes vary some variants seem similar between *HLA-DRB1*1101* is reported as risk

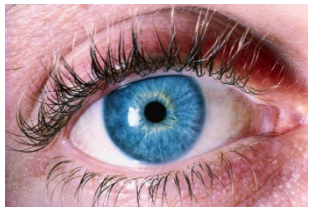
Kopplat till kronisk sjukdom

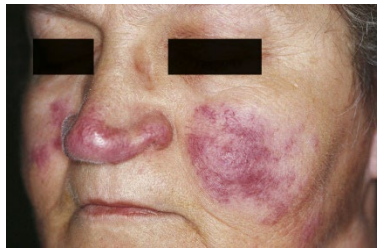
Kopplat till dålig effekt av kortison

Var är de?

Parameter	Pat m lymfopeni i blod	Pat m normalt antal lymfocyter i blod
Median antal lymfocyter i lungan (x10^6/l)	37 (23-83)	40 (25-66)



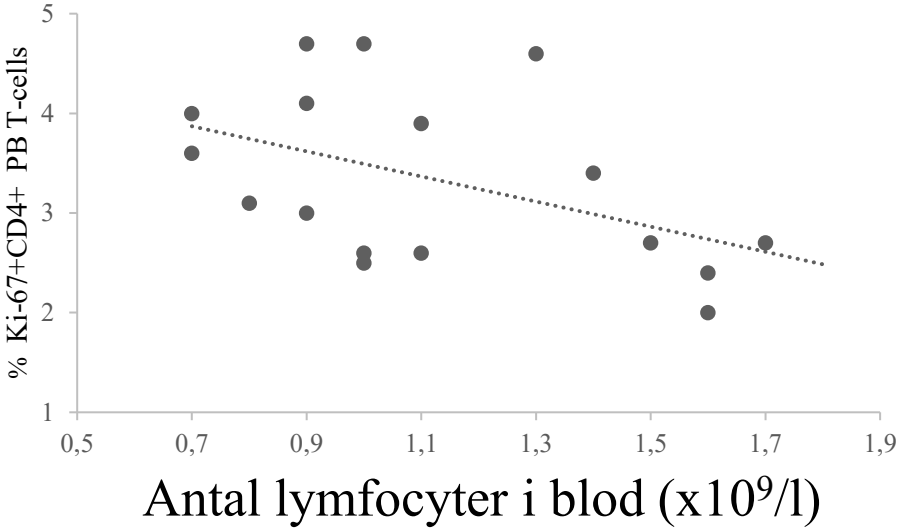


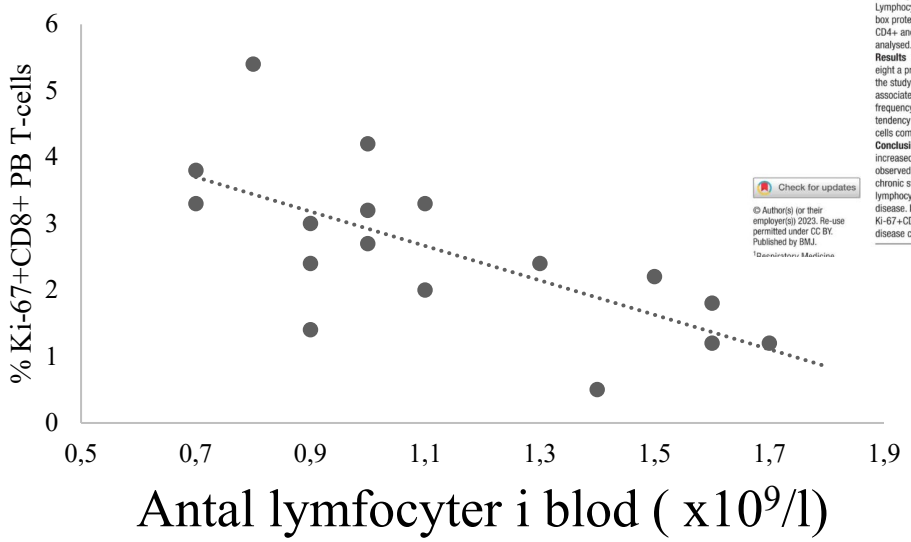


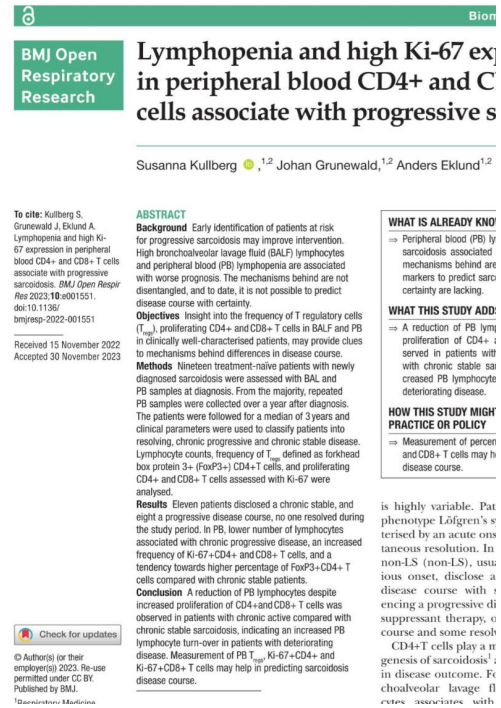
Parameter	Pat m lymfopeni i blod	Pat m normalt antal lymfocyter i blod
% av antal patienter med EPM	44%	44%

Var är de?

Och…de delar sig






BMJ Open Respiratory Research

Lymphopenia and high Ki-67 ex
in peripheral blood CD4+ and C
cells associate with progressive s

Susanna Kullberg ,[1,2] Johan Grunewald,[1,2] Anders Eklund[1,2]

To cite: Kullberg S, Grunewald J, Eklund A. Lymphopenia and high Ki-67 expression in peripheral blood CD4+ and CD8+ T cells associate with progressive sarcoidosis. *BMJ Open Respir Res* 2023;**10**:e001551. doi:10.1136/bmjresp-2022-001551

Received 15 November 2022
Accepted 30 November 2023

Check for updates

© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY. Published by BMJ.

ABSTRACT

Background Early identification of patients at risk for progressive sarcoidosis may improve intervention. High bronchoalveolar lavage fluid (BALF) lymphocytes and peripheral blood (PB) lymphopenia are associated with worse prognosis. The mechanisms behind are not disentangled, and to date, it is not possible to predict disease course with certainty.

Objectives Insight into the frequency of T regulatory cells (T_{reg}), proliferating CD4+ and CD8+ T cells in BALF and PB in clinically well-characterised patients, may provide clues to mechanisms behind differences in disease course.

Methods Nineteen treatment-naïve patients with newly diagnosed sarcoidosis were assessed with BAL and PB samples at diagnosis. From the majority, repeated PB samples were collected over a year after diagnosis. The patients were followed for a median of 3 years and clinical parameters were used to classify patients into resolving, chronic progressive and chronic stable disease. Lymphocyte counts, frequency of T_{reg} defined as forkhead box protein 3+ (FoxP3+) CD4+T cells, and proliferating CD4+ and CD8+ T cells assessed with Ki-67 were analysed.

Results Eleven patients disclosed a chronic stable, and eight a progressive disease course, no one resolved during the study period. In PB, lower number of lymphocytes associated with chronic progressive disease, an increased frequency of Ki-67+CD4+ and CD8+ T cells, and a tendency towards higher percentage of FoxP3+CD4+ T cells compared with chronic stable patients.

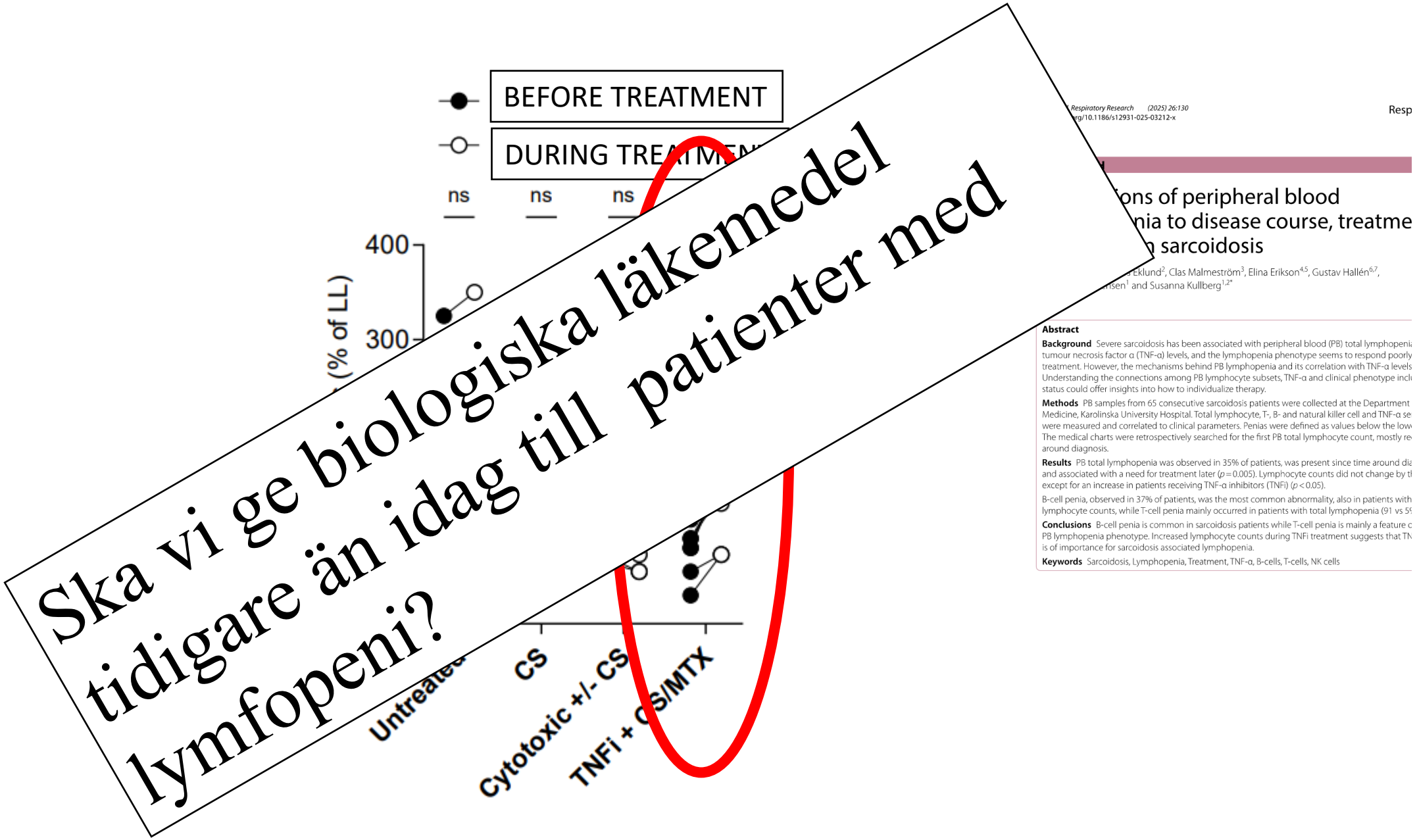
Conclusion A reduction of PB lymphocytes despite increased proliferation of CD4+and CD8+ T cells was observed in patients with chronic active compared with chronic stable sarcoidosis, indicating an increased PB lymphocyte turn-over in patients with deteriorating disease. Measurement of PB T_{reg}, Ki-67+CD4+ and Ki-67+CD8+ T cells may help in predicting sarcoidosis disease course.

WHAT IS ALREADY KNO
⇒ Peripheral blood (PB) ly
sarcoidosis associated
mechanisms behind are
markers to predict sarc
certainty are lacking.

WHAT THIS STUDY ADD
⇒ A reduction of PB lym
proliferation of CD4+
served in patients with
with chronic stable sa
creased PB lymphocyte
deteriorating disease.

HOW THIS STUDY MIGH
PRACTICE OR POLICY
⇒ Measurement of percen
and CD8+ T cells may h
disease course.

is highly variable. Pat
phenotype Löfgren's s
terised by an acute ons
taneous resolution. In
non-LS (non-LS), usu
ious onset, disclose a
disease course with
encing a progressive di
suppressant therapy,
course and some resol
CD4+T cells play a
genesis of sarcoidosis
in disease outcome. Fo
choalveolar lavage fl
cytes associates with



Ska vi ge biologiska läkemedel tidigare än idag till patienter med lymfopeni?

Respiratory Research (2025) 26:130
rg/10.1186/s12931-025-03212-x

Resp

ons of peripheral blood
nia to disease course, treatme
n sarcoidosis

Eklund[2], Clas Malmeström[3], Elina Erikson[4,5], Gustav Hallén[6,7],
nsen[1] and Susanna Kullberg[1,2*]

Abstract

Background Severe sarcoidosis has been associated with peripheral blood (PB) total lymphopeni
tumour necrosis factor α (TNF-α) levels, and the lymphopenia phenotype seems to respond poorly
treatment. However, the mechanisms behind PB lymphopenia and its correlation with TNF-α levels
Understanding the connections among PB lymphocyte subsets, TNF-α and clinical phenotype incl
status could offer insights into how to individualize therapy.

Methods PB samples from 65 consecutive sarcoidosis patients were collected at the Department
Medicine, Karolinska University Hospital. Total lymphocyte, T-, B- and natural killer cell and TNF-α se
were measured and correlated to clinical parameters. Penias were defined as values below the low
The medical charts were retrospectively searched for the first PB total lymphocyte count, mostly re
around diagnosis.

Results PB total lymphopenia was observed in 35% of patients, was present since time around dia
and associated with a need for treatment later ($p = 0.005$). Lymphocyte counts did not change by t
except for an increase in patients receiving TNF-α inhibitors (TNFi) ($p < 0.05$).

B-cell penia, observed in 37% of patients, was the most common abnormality, also in patients with
lymphocyte counts, while T-cell penia mainly occurred in patients with total lymphopenia (91 vs 5

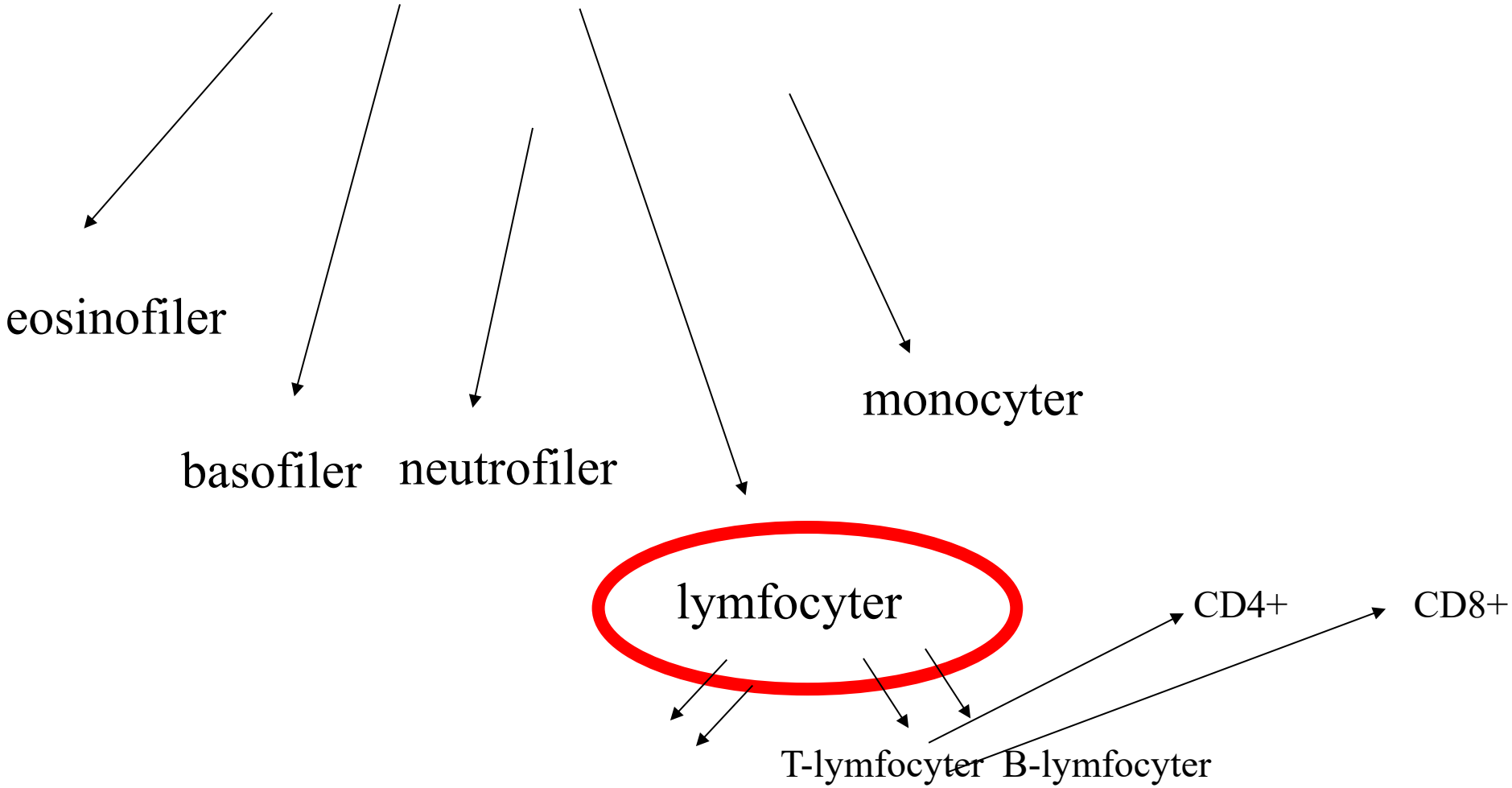
Conclusions B-cell penia is common in sarcoidosis patients while T-cell penia is mainly a feature c
PB lymphopenia phenotype. Increased lymphocyte counts during TNFi treatment suggests that TN
is of importance for sarcoidosis associated lymphopenia.

Keywords Sarcoidosis, Lymphopenia, Treatment, TNF-α, B-cells, T-cells, NK cells

Var är de?

Några misstankar

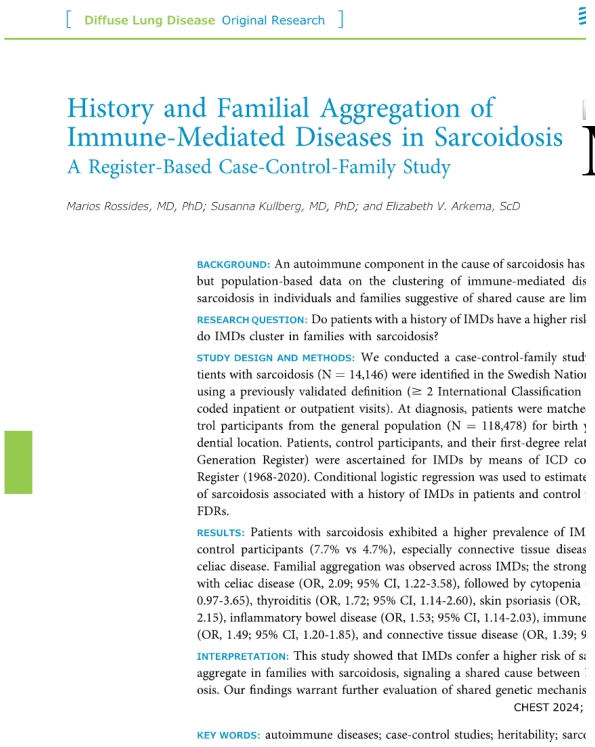
VITA BLODKROPPAR



Varför har jag hakat upp mig på lymfocyter?

Myositpatienter har låga lymfocyter i blod

Pan et al., 2025, dÁlessandro et al., 2023



[Diffuse Lung Disease Original Research]

History and Familial Aggregation of Immune-Mediated Diseases in Sarcoidosis

A Register-Based Case-Control-Family Study

Marios Rossides, MD, PhD; Susanna Kullberg, MD, PhD; and Elizabeth V. Arkema, ScD

BACKGROUND: An autoimmune component in the cause of sarcoidosis has
but population-based data on the clustering of immune-mediated dis
sarcoidosis in individuals and families suggestive of shared cause are lim

RESEARCH QUESTION: Do patients with a history of IMDs have a higher risl
do IMDs cluster in families with sarcoidosis?

STUDY DESIGN AND METHODS: We conducted a case-control-family stud
tients with sarcoidosis (N = 14,146) were identified in the Swedish Natio
using a previously validated definition (≥ 2 International Classification
coded inpatient or outpatient visits). At diagnosis, patients were matche
trol participants from the general population (N = 118,478) for birth
dential location. Patients, control participants, and their first-degree relat
Generation Register) were ascertained for IMDs by means of ICD co
Register (1968-2020). Conditional logistic regression was used to estimate
of sarcoidosis associated with a history of IMDs in patients and control
FDRs.

RESULTS: Patients with sarcoidosis exhibited a higher prevalence of IM
control participants (7.7% vs 4.7%), especially connective tissue diseas
celiac disease. Familial aggregation was observed across IMDs; the strong
with celiac disease (OR, 2.09; 95% CI, 1.22-3.58), followed by cytopenia
0.97-3.65), thyroiditis (OR, 1.72; 95% CI, 1.14-2.60), skin psoriasis (OR,
2.15), inflammatory bowel disease (OR, 1.53; 95% CI, 1.14-2.03), immune
(OR, 1.49; 95% CI, 1.20-1.85), and connective tissue disease (OR, 1.39; 9

INTERPRETATION: This study showed that IMDs confer a higher risk of s
aggregate in families with sarcoidosis, signaling a shared cause between
osis. Our findings warrant further evaluation of shared genetic mechanis

CHEST 2024;

KEY WORDS: autoimmune diseases; case-control studies; heritability; sarc

Myositpatienter har nästan 4 ggr ökad risk för sarkoidos.

Så enkelt är det tyvärr i …..

- Lymfopeni ses även vi… sjukd…
- Sarkoidospatient… ökad ri… massvis av ar… domar

HIV patien… låga lymfocyter i blod

Patienter med … låga lymfocyter i blod

Vid flera autoimmuna … låga lymfocyter i blod

3 ggr ökad risk för glutenintolerans

2 ggr ökad risk för psoriasisarthrit

Men….

- Risken för sarkoidos är särskilt hög vid myosit
- Lymfopenimönstret vid myosit liknar det vid sarkoidos

Vi gräver nu vidare…..

Tips tas tacksamt emot

Ett stort tack till alla givare:
Hjärt-Lungfonden
Vetenskapsrådet
Region Stockholm (ALF, Högre klinisk forskare)

MYOSIT- OCH SARKOIDOSINITIATIVET