The Search for Berylliosis in Israel: First Five Years (1999-2004)

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ISRAEL
Beryllium Induced Diseases in Israel

Case Communication

Beryllium disease: first reported case in Israel

Fireman E, Kramer MR, Kaufman N, Muller-Quernheim J, Lerman Y.

Case report I

October 1998
27 year old white female
Past medical history: no serious illness
Occupation: 1994-1997 dental technician

March 1998
shortness of breath, weakness, nausea, vomiting, diarrhea, weight loss (12 kg).
3/1998: emergency room visit, normal chest X rays, referred to a Psychiatrist, treated by prozac.

December 1998
deterioration of her symptoms
Chest X rays: increased interstitial pattern, hylar lympho adenopathy
Laboratory findings

- **Biochemical Parameters**
  - SGOT (0-37): 161
  - SGPT (0-43): 126
  - LDH (230-460): 1210

- **Blood Gases**
  - pCO₂: 38.9
  - pO₂: 67.0

- **Serological parameters**
  - (-)

- **Hematological Parameters**
  - WBC (4.5-10.5): 11.4
  - ESR (1hr): 50

- **Immunological Parameters**
  - HIV, HCV, HBsAg (-)

- **Urine**
  - normal

- **PPD**
  - (-)
Final Diagnosis and Management

- Final diagnosis of Sarcoidosis was confirmed by OLB.
- Tissue analysis showed abundant non caseating granulomas.
- Treatment: Corticosteroid therapy was instituted.
- Due to occupational history, she was referred to our laboratory.
Work-up by Laboratory of Pulmonary Diseases Tel-Aviv Medical Center.

✓ PFT
✓ INDUCED SPUTUM
✓ SEM
✓ BeLPT
Induced Sputum (SEM)

Particles Analysis

- $\text{Al}_2\text{Si}_4(\text{OH})_2$
- Al Si Ca
- Al Si Fe
- $\text{SiO}_2$
- $\text{CaCO}_3$
- $\text{CaMg}(\text{CO}_3)_2$
- $\text{Fe}_2\text{O}_3$
BELPT = Beryllium Lymphocyte Proliferation Test

![Graph showing stimulation index of Be2 SO4 at different concentrations.](image-url)
The next step was to test the hypothesis that other cases of CBD in Israel were not previously reported because these patients were misdiagnosed as having SA.

METHODS: Forty-seven patients with confirmed-SA from our outpatient clinic were recalled in order to reevaluate their occupational exposure history.

We performed the beryllium lymphocyte proliferation test (BeLPT) on each patient with a potentially positive environmental exposure anamnesis to beryllium.

Supported by Israel Chief Scientist Office-Ministry of Health
Table I: Demographic and clinical parameters of the study population

<table>
<thead>
<tr>
<th>Study population</th>
<th>Women (n)</th>
<th>Men (n)</th>
<th>Age range (y)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with occupational history of beryllium exposure</td>
<td>26</td>
<td>21</td>
<td>29-79</td>
<td>47</td>
</tr>
<tr>
<td>Sarcoidosis staging by chest X-ray</td>
<td>4</td>
<td>10</td>
<td>40-69</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>n=3</td>
</tr>
<tr>
<td>Stage I</td>
<td>n=10</td>
</tr>
<tr>
<td>Stage II</td>
<td>n=24</td>
</tr>
<tr>
<td>Stage III</td>
<td>n=8</td>
</tr>
<tr>
<td>Stage IV</td>
<td>n=2</td>
</tr>
</tbody>
</table>
Results: 3/14 positive BELPT

✓ 3/14 who all had a positive occupational exposure to beryllium.

✓ 2/14 patients with evidence of granulomas in lung tissue (pulmonary involvement).

✓ 1/14 with extra pulmonary involvement.
Case report 1

✓ This 40-year-old non-smoker woman had worked as a mechanical engineer from 1986-1996

✓ HRCT showed bilateral hilar lymphadenopathy, ACE test was 111 nM/cc/min (normal = 45-125),

✓ BAL+TBB showed non-caseating granulomas, and the CD4/CD8 ratio was 6.2 (normal = 1.0-2.5). The patient was diagnosed as suffering from SA and corticosteroid therapy was instituted.

✓ The occupational history revealed that she had worked at a factory that produced turbines for power plants and was involved with the soldering, polishing, and grinding of metals. The BeLPT test was positive.
Case report 2

✓ During an evaluation of cardiac arrhythmia of this 61-year-old non-smoker man.
✓ HRCT revealed an micronodular pattern with bilateral hilar lymphadenopathy.
✓ TBB was compatible with granulomatous lesions. The CD4/CD8 ratio was 5.13. He was diagnosed as having SA and appropriate therapy was instituted.
✓ In response to the questionnaire of the present study, it emerged that he had a past occupational history of cutting metal plates with exposure to a dusty environment without protective equipment. He worked also as a mechanical engineer with textile machines, again without safety measures against inhaling dust. His BeLPT test was positive
This 32-year-old non-smoker working for 16 years as a dental technician. Four years before he had complained of recurrent anterior uveitis. The chest X-ray was normal. The ACE test was 219 n M/cc/min.

TBB+BAL was not performed for ethical reasons.

Induced sputum analysis revealed lymphocytosis and a CD4/CD8 ratio of 5.1. In light of his past exposure to Be and his employment as a dental technician, a BeLPT tests was positive.
Beryllium Induced Diseases in Israel 1999-2004

We tested a total of 35 patients

12 BELPT positive
23 BELPT negative

Routine work-up
1. Occupational History
2. X-rays and HRCT
3. PFT
4. TBB+BAL
5. BELPT
6. Induced Sputum (Differential Counts and CD4/CD8 ratio)
### Beryllium Induced Diseases in Israel 2004

12 patients with CBD

<table>
<thead>
<tr>
<th>Occ</th>
<th>Belpt</th>
<th>IS</th>
<th>CD4/CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dental T</td>
<td>(+)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2. Dental T</td>
<td>(+)</td>
<td>(+)</td>
<td>14.6</td>
</tr>
<tr>
<td>3. Dental T</td>
<td>(+)</td>
<td>(+)</td>
<td>12.8</td>
</tr>
<tr>
<td>4. Dental T</td>
<td>(+)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5. Dental T</td>
<td>(+)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>6. Dental T</td>
<td>(+)</td>
<td>(+)</td>
<td>5.4</td>
</tr>
<tr>
<td>7. Dental T</td>
<td>(+)</td>
<td>(+)</td>
<td>5.6</td>
</tr>
<tr>
<td>8. Metal W</td>
<td>(+)</td>
<td>(+)</td>
<td>4.6</td>
</tr>
<tr>
<td>9. Chernobill</td>
<td>(+)</td>
<td>(+)</td>
<td>4</td>
</tr>
<tr>
<td>10. Floresent</td>
<td>(+)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>11. Battery Factory</td>
<td>(+)</td>
<td>(+)</td>
<td>4.75</td>
</tr>
<tr>
<td>12. Airplaine I</td>
<td>(+)</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>
Why to perform CD4/CD8 ratio in sputum???

- We proposed that this parameter can surrogate the use of BAL +TBB.
- CD4/CD8 ratio in sputum is a marker of GRANULOMATOSIS.
We have already demonstrated the utility of Induced Sputum in the diagnosis of
Granulomatous Diseases.

- Induced sputum compared to bronchoalveolar lavage for evaluating patients with sarcoidosis and non-granulomatous interstitial lung disease. 

- The use of induced sputum in the assessment of pulmonary involvement in Crohn's disease.

- Induced sputum for identifying sarcoidosis in patients with uveitis.

- Induced sputum to identify a Melkerson-Rosenthal syndrome granulomatosis.
  E Fireman S Kivity Submitted for publication.
Why analysis of T cell lymphocytes in Induced Sputum can identify pulmonary and extrapulmonary granulomatosis?
CD4 circulation

Reinhard Pabst

Non invasive approach in the diagnosis of Sarcoidosis

Elizabeth Fireman.1,2, Tatiana Boikaner.1,2 Yehuda Schwartz.1,2 Abraham Man.1,2 Joel Greif.1,2 1Pulmonary and Allergic Dis, Tel-Aviv Medical Center, Tel-Aviv, Israel; 2Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel

Submitted for Publication

We evaluated 120 pts; 67 SA and 53 NSA

ILD

In a non invasive approach using parameters as IS and PFT that can be used as predictors with high specificity and sensitivity in the differential diagnosis of SA.
**ROC curve showing specificity and sensitivity of model 1 - Gender, Age, Smoking, CD4/CD8, Eosinophils and neutrophils as explanatory variables**

![ROC Curve](image)

<table>
<thead>
<tr>
<th>Variable(s)</th>
<th>P value</th>
<th>Odd ratio</th>
<th>Ranges</th>
<th>Area under the curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender</td>
<td>0.196</td>
<td>0.507</td>
<td>0.181</td>
<td>1.419</td>
</tr>
<tr>
<td>Age</td>
<td>0.004</td>
<td>0.940</td>
<td>0.901</td>
<td>0.981</td>
</tr>
<tr>
<td>smoking</td>
<td>0.314</td>
<td>0.446</td>
<td>0.092</td>
<td>2.149</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>0.000</td>
<td>1.742</td>
<td>1.334</td>
<td>2.276</td>
</tr>
<tr>
<td>Eos</td>
<td>0.048</td>
<td>0.932</td>
<td>0.869</td>
<td>0.999</td>
</tr>
<tr>
<td>Neutro</td>
<td>0.055</td>
<td>0.978</td>
<td>0.955</td>
<td>1.001</td>
</tr>
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</table>

Table 1
**ROC curve showing specificity and sensitivity of model 2 - gender, age, smoking, CD4/CD8, RV, TLC Eosinophils and neutrophils as explanatory variables**

<table>
<thead>
<tr>
<th>Variable(s)</th>
<th>P value</th>
<th>Odd ratio</th>
<th>Ranges</th>
<th>Area under the curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.138</td>
<td>0.397</td>
<td>0.117</td>
<td>1.344</td>
</tr>
<tr>
<td>Age</td>
<td>0.013</td>
<td>0.942</td>
<td>0.899</td>
<td>0.987</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.923</td>
<td>0.922</td>
<td>0.176</td>
<td>4.775</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>0.000</td>
<td>1.958</td>
<td>1.400</td>
<td>2.739</td>
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<tr>
<td>RV</td>
<td>0.000</td>
<td>0.941</td>
<td>0.911</td>
<td>0.973</td>
</tr>
<tr>
<td>TLC</td>
<td>0.006</td>
<td>1.079</td>
<td>1.022</td>
<td>1.140</td>
</tr>
</tbody>
</table>

Table 2
### Beryllium Induced Diseases in Israel 2004

23 patients negative BELPT

<table>
<thead>
<tr>
<th>Occ</th>
<th>Belpt</th>
<th>Diagnosis</th>
<th>IS</th>
<th>CD4/CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dental T</td>
<td>(-)</td>
<td>SA</td>
<td>(+)</td>
<td>1.34</td>
</tr>
<tr>
<td>2. Dental T</td>
<td>(-)</td>
<td>SA</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3. Dental T</td>
<td>(-)</td>
<td>SA</td>
<td>(+)</td>
<td>0.2</td>
</tr>
<tr>
<td>4. Dental T</td>
<td>(-)</td>
<td>SA</td>
<td>(+)</td>
<td>13.8</td>
</tr>
<tr>
<td>5. Dental T</td>
<td>(-)</td>
<td>SA</td>
<td>(+)</td>
<td>3.24</td>
</tr>
<tr>
<td>6. Dental T</td>
<td>(-)</td>
<td>SA</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7. Dental T</td>
<td>(-)</td>
<td>Lymphoma</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8. Dental T</td>
<td>(-)</td>
<td>Hepatomegaly</td>
<td>(+)</td>
<td>1.21</td>
</tr>
<tr>
<td>9. Dental T</td>
<td>(-)</td>
<td>IPF Transplantation</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>10. Dental T</td>
<td>(-)</td>
<td>uveitis</td>
<td>(+)</td>
<td>4.8</td>
</tr>
<tr>
<td>11. Metal W</td>
<td>(-)</td>
<td>DIF</td>
<td>(+)</td>
<td>1.36</td>
</tr>
<tr>
<td>12. Metal W</td>
<td>(-)</td>
<td>DIF</td>
<td>(+)</td>
<td>4.2</td>
</tr>
<tr>
<td>13. Metal W</td>
<td>(-)</td>
<td>DIF</td>
<td>(+)</td>
<td>0.36</td>
</tr>
<tr>
<td>14. Metal W</td>
<td>(-)</td>
<td>reiter Sy-uv</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>15. Metal W</td>
<td>(-)</td>
<td>SA</td>
<td>(+)</td>
<td>6.36</td>
</tr>
<tr>
<td>16. Metal W</td>
<td>(-/+)</td>
<td>SA</td>
<td>(+)</td>
<td>3.7</td>
</tr>
<tr>
<td>17. Metal W</td>
<td>(-)</td>
<td>SA</td>
<td>(+)</td>
<td>7.92</td>
</tr>
<tr>
<td>18. Al exp</td>
<td>(-)</td>
<td>SA</td>
<td>(+)</td>
<td>ND</td>
</tr>
<tr>
<td>19. Al exp</td>
<td>(-)</td>
<td>SA</td>
<td>(+)</td>
<td>9.7</td>
</tr>
<tr>
<td>20. Electrician</td>
<td>(-)</td>
<td>SA</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>21. Building</td>
<td>(-)</td>
<td>DIF</td>
<td>(+)</td>
<td>3.45</td>
</tr>
<tr>
<td>22. Building</td>
<td>(-)</td>
<td>DIF</td>
<td>(+)</td>
<td>2.8</td>
</tr>
<tr>
<td>23. Chernobill</td>
<td>(-)</td>
<td>uveitis</td>
<td>(+)</td>
<td>2.7</td>
</tr>
</tbody>
</table>
Beryllium Induced Diseases in Israel
2004........ Follow-up

✓ Noting that most of berylliosis patients were dental technicians, the use of beryllium for dental tools has been banned in Israel (by the Israeli Ministry of Health and Ministry of Industry, Trade and Labor).

✓ In 2004, we checked whether the law regarding importation of the metal is being enforced and to what extent dental laboratories continue to work with it.

✓ We were appalled to find that beryllium continues to be the most ubiquitous metal in the profession.
Following our shocking discovery, we recruited our first berylliosis patient and a local journalist and succeeded in gaining national exposure of the situation.
This health issue was raised in The (Israel’s legislative body) Knesset
Beryllium Induced Diseases in Israel 2004 Follow-up

- The following operative decisions were taken:
  - To institute a national questionnaire for sarcoid patients (to avoid misdiagnosis with berylliosis)
  - To tighten the regulations on the use of beryllium in Israel
  - To check the extent of beryllium use in other industries (military, nuclear, etc.)
Induced sputum as an additional tool in the identification of metal-induced sarcoid-like reaction

Sarcoidosis Vasc Diffuse Lung Dis. 2004 21(2):152-6

✓ A 43-year-old male former smoker presented with a 3-month history of dyspnea without cough, weight loss or fatigue.

✓ He had been working as a welder for more than 20 years in different industries where he had been exposed mostly to stainless steel and nonferrous alloys.

✓ Chest X ray showed bilateral lymphadenopathy with diffuse reticulonodular infiltration. HRCT showed small, well-defined micronodules.

✓ Guided CT biopsy showed abundant noncaseating granulomata.
1. In light of his past occupational history, he was referred to our clinic to rule out berylliosis.

2. The patient underwent BeLPT twice and there were borderline stimulation index values both times.

3. In order to differentiate between sarcoid and non-beryllium metal-induced granulomatosis, we carried out induced sputum for mineralogical studies.
Induced sputum as an additional tool in the identification of metal-induced sarcoid-like reaction

Results

Mineralogical studies were performed on induced sputum sample and then on the paraffin block of the biopsy. We found mainly the presence of ALUMINIUM.
INDUCED SPUTUM
Induced sputum as an additional tool in the identification of metal-induced sarcoid-like reaction

<table>
<thead>
<tr>
<th>Cells</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>70</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>5</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>17</td>
</tr>
<tr>
<td>Macrophages</td>
<td>8</td>
</tr>
<tr>
<td>CD4 lymphocytes</td>
<td>41.7</td>
</tr>
<tr>
<td>CD8 lymphocytes</td>
<td>12.0</td>
</tr>
<tr>
<td>CD4/CD8 ratio</td>
<td>3.47 (N=1-2.5)</td>
</tr>
</tbody>
</table>
Induced sputum as an additional tool in the identification of metal-induced reaction

<table>
<thead>
<tr>
<th>Controls (n=4) cpm</th>
<th>Controls (n=4) cpm</th>
<th>Patient (n=1) cpm</th>
<th>Patient (n=1) cpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>534±122</td>
<td>200±29</td>
<td>2049±611</td>
<td>4554±1473</td>
</tr>
<tr>
<td>435±187</td>
<td>329±72**</td>
<td>2279±547</td>
<td>14450±2404**</td>
</tr>
<tr>
<td>423±161</td>
<td>451±100**</td>
<td>2310±548</td>
<td>6976±1277**</td>
</tr>
<tr>
<td>428±126</td>
<td>373±100**</td>
<td>2182±611</td>
<td>7956±1950**</td>
</tr>
<tr>
<td>620±71</td>
<td>200±29</td>
<td>2049±611</td>
<td>5480±1329</td>
</tr>
<tr>
<td>651±58</td>
<td>422±146**</td>
<td>1644±632</td>
<td>10080±1453**</td>
</tr>
<tr>
<td>319±50</td>
<td>464±163**</td>
<td>2794±1125</td>
<td>9912±2344**</td>
</tr>
<tr>
<td>400±47</td>
<td>365±115**</td>
<td>1841±1150</td>
<td>7008±2053**</td>
</tr>
</tbody>
</table>

Bl

AlCl₃-1 µg

7008±2053**

1841±1150

365±115**

400±47

AlCl₃-10 µg

2794±1125

1841±1150

365±115**

400±47

AlCl₃-100 µg

2279±547

1841±1150

365±115**

400±47

AlSO₄-100 µg

2182±611

1841±1150

365±115**

400±47

AlSO₄-1 µg

2310±548

1841±1150

365±115**

400±47

AlSO₄-10 µg

2310±548

1841±1150

365±115**

400±47

** p<0.01
Clinical Manifestation

Occupational History

X-Rays and HRCT

Induced Sputum Differential Counts

Positive occupational history, bilateral lymphoadenopathy, interstitial infiltrates, lymphocytosis with high CD4/CD8 ratio in sputum, evidence of high load of particles in sputum macrophages

BELPT in peripheral blood lymphocytes

Negative or borderline

SEM IN INDUCED SPUTUM for mineralogical studies

Identification of antigenic metal i.e. aluminum

Metal- induced sarcoid- like reaction

Blastic transformation of peripheral blood lymphocytes with identified metal

Granulomatous diseases of unidentified origin

(-)
The future Search for Berylliosis in Israel: 2005....

- A screening program for 3000 dental technicians.
- Search of other potential industries.
- Avoidance of future exposures.
The future Search for Berylliosis in Israel: 2005...

thank you
merci
谢谢
danke
شكرا
どうもありがとうございました
gracias