Clinical studies and tissue analyses in the earliest phases of rheumatoid arthritis: In search of the transition from being at risk to having clinically apparent disease

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HUNTING FOR THE PATHOGENESIS OF RHEUMATOID ARTHRITIS: CORE-NEEDLE BIOPSY OF INGUINAL LYMPH NODES AS A NEW RESEARCH TOOL

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Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease affecting mainly the synovial joints. Processes involved in the initiation of inflammation in RA are largely unknown. Recent work has shown that systemic autoimmunity precedes synovial inflammation in autoantibody positive individuals developing RA\(^1\) and animal models have suggested that lymph node changes may precede inflammation in the synovial tissue\(^2\). Ultrasound guided lymph node biopsy under local anesthesia has previously been used as a diagnostic tool in hematology and oncology\(^3\). Therefore, we started to use this technique to provide insight into the pathogenic processes involved in the earliest phases of RA, by analyzing lymph node tissue obtained during different phases of the disease. Our experience includes use of this technique in autoantibody positive individuals without arthritis who are at risk of developing RA\(^4\), early arthritis patients and established RA patients. The studies have been approved by the institutional review board of the Academic Medical Center/University of Amsterdam. Here we describe the technique and the initial experience, which may facilitate research in other centres. Study candidates are informed about the background and purpose of the study and the biopsy procedure and possible complications (in particular hematoma). Written informed consent is obtained. Anticoagulant therapy is stopped. The lymph node biopsy procedure is performed on an inguinal lymph node in an outpatient clinical setting by a radiologist and assistant, see Figure 1.

**Figure 1.** Ultrasound guided core-needle biopsy procedure of an inguinal lymph node. A. Utensils are placed on a sterile table B. A bar gun is used to obtain biopsies under ultrasound guiding C. Ultrasound image of the biopsy needle within the lymph node D. The biopsy is placed on a wet gauze E. The biopsy is put in medium.
We select a lymph node from the ipsilateral side in case of arthritis of the knee or ankle joint. In other cases the most easily accessible lymph node is selected as shown by ultrasound examination using a 17MHz linear probe (Philips IU22 ultrasound system). A sterile field is created and the ultrasound probe is covered by a sterile sheet. Local anesthesia is obtained using 8-10cc 2% lidocaine and a 0.5cm incision is made. Five to 6 biopsies are obtained using a semi-automated biopsy gun (Bard Magnum reusable core biopsy system) and a Bard Magnum disposable core tissue biopsy needle, 16G x 13 cm. Ultrasound guiding makes it a safe and accurate procedure and allows us to obtain representative biopsies along the full length of the lymph node. Manual pressure is applied to the biopsied area after each biopsy and at the end of the procedure for 2 minutes to reduce hematoma formation. The wound is closed using adhesive plaster. No precautions need to be taken afterwards. The total procedure takes about 25 minutes.

Biopsy samples are collected on non-woven, wet gauzes and immediately processed by a laboratory technician. Single biopsies are either snap-frozen in Tissue-Tek OCT (Miles, Elkhart, IN) for immunohistochemistry, snap-frozen for RNA isolation or placed in medium for FACS analysis. Comparable sample handling has previously been described in detail for synovial tissue biopsies. The samples are currently used for FACS analysis and microarray analysis. The amount and quality of the tissue provides good RNA yield and reliable FACS analysis data (data not shown).

We have included 79 subjects who underwent lymph node biopsy sampling of whom 32 underwent a follow-up biopsy after one year to evaluate changes over time. Generally, the procedure was well tolerated. See Table 1 for an overview of the complications observed. One subject presenting with a reactive lymph node after the biopsy procedure underwent a follow-up biopsy without any complications. In conclusion, our experience shows for the first time that ultrasound guided lymph node biopsy sampling is a feasible new research tool for studying RA pathogenesis.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Short period of pain in the groin</td>
<td>7%</td>
</tr>
<tr>
<td>Persistent pain for two months</td>
<td>0.9%</td>
</tr>
<tr>
<td>Persistent pain and swelling for 3 weeks due to reactive lymph node</td>
<td>0.9%</td>
</tr>
<tr>
<td>Hematoma</td>
<td>80%</td>
</tr>
</tbody>
</table>

Frequency: frequency of total procedures performed.

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REFERENCE LIST


