Transbronchial Cryobiopsy in unexplained, severe ARDS – a single center retrospective case series

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Abstract

Background: Acute respiratory distress syndrome (ARDS) is a common cause of severe respiratory impairment. It needs a correct characterization which often is challenging. Additional surgical lung biopsy was previously reported to be of additive value. In severe and unexplained ARDS we tried to define an additional diagnostic benefit of transbronchial cryobiopsy (TBCB).

Method: We retrospectively collected data of TBCB in unexplained ARDS, whether with or without ECMO-support. TBCB was performed in one segment, that was prophylactically occluded by Watanabe spigot or swab after the procedure. Histology results and their contribution to further therapeutic decisions were analyzed.

Results: Between 2019 and 2020 TBCB was performed in seven patients. Decision for the intervention was decided in multidisciplinary discussion before. Three patients were treated with ECMO. The median duration of invasive ventilation before TBCB was 24 days. Histology revealed four diffuses alveolar damage, one acute fibrinoid organizing pneumonia and one cryptogenic organizing pneumonia. All results contributed to the decision of further management. While no pneumothorax or severe endobronchial bleeding occurred, two delayed hematothoraces needed surgical treatment. No patients died due to TBCB.

Conclusion: TBCB is feasible in ARDS even during ECMO treatment. Histologic results can play a significant role in therapeutic and ethic discussion to guide the patients' path. Side effects should be considered and monitored.

Introduction

Acute respiratory distress syndrome (ARDS) is a common cause of severe respiratory impairment. The diagnosis consists of clinical and radiological features. Several aetiologies of ARDS can be distinguished, the respective underlying cause influences the individual treatment strategy. Correct identification and early treatment are crucial for ARDS outcome [1].

Beside identification of patients' intrinsic risk factors a multi-modal diagnostic approach is essential. Based on radiological criteria methods of interventional bronchology might be of additional use, if necessary. Tissue based diagnosis was described as helpful when performed by open lung biopsy but with relevant amount of side effects [2]. Bronchoscopic tissue collection by forceps biopsy in interstitial lung disease (ILD) is reported to have only a small diagnostic yield [3]. Therefore, other methods need to be investigated.

We describe our experience with transbronchial cryobiopsy (TBCB), a method that was introduced into the diagnosic workup of unexplained interstitial lung disease (ILD), in our patients with unexplained severe ARDS with dependency on mechanical ventilation with or without extra corporal membrane oxygenation (ECMO).

Materials And Methods

We retrospectively analyzed our single center case series of patients suffering from unexplained hypoxemic respiratory failure that meet the Berlin criteria of acute respiratory distress syndrome (ARDS) from June 2019 to August 2020. Our tertiary referral center provides a specialized extra-corporal membrane oxygenation (ECMO) programme for an area of approximately three million inhabitants. The department of interventional pulmonology has profound knowledge in TBCB either in the work up of ILD or in diagnosis and therapy lung cancer.

Inclusion criteria were (1) underlying unexplained ARDS based on Berlin definition with clinical and radiological interpretation, (2) current high resolution computed tomography (HR-CT) of the lung, (3) exclusion of a persistent or predominant infectious ARDS cause based on previous investigation including bronchioalveolar lavage (BAL), (4) multidisciplinary discussion claimed for additional tissue sampling to understand the cause and prognosis of the individual patients' ARDS, (5) individual informed consent to the TBCB given by legal representatives and (6) no severe additional condition that does not allow the performance of TBCB.

Treatment with extracorporal membrane oxygenation (ECMO) was not an exclusion criterion. Effective anticoagulation therapy was paused or reduced, if possible.

TBCB was performed as previously recommended [4, 5]. Shortly, a flexible bronchoscope (Olympus, 2.8 mm working channel, Japan) was inserted during rigid bronchoscopy (Storz, Tuebingen, Germany) or the established endotracheal tube. Ventilatory support was dependent on the respective approach. A flexible 1.9 mm cryoprobe (ERBE, Tuebingen, Germany) was inserted through the working channel into the subpleural zone of the lung periphery, controlled with fluoroscopy whenever possible (Fig. 1). Biopsy was taken only from one pulmonary segment to minimize bleeding complications. The biopsy location was previously selected with regard to the High resoluted (HR) -CT and simple endoscopic access. The maximum freezing time was agreed with five seconds, a total amount of 3 visible tissue specimen were extracted and placed into formalin. Tissue specimen were processed and investigated in the Institute of Pathology of the university of Halle-Wittenberg.

After every biopsy segmental suction was done (ZAVALA manoeuvre). A prophylactic balloon blockade during bronchoscopy was not regularly used, but after TBCB the selected segment was blocked with swabs or Watanabe-Spigot (Novatech, Lyon, France), depending on the individual anatomy for 48 hours and removed in a consecutive flexible bronchoscopy.

Pneumothorax exclusion was performed by transthoracic ultrasound (TUS) immediately after the procedure and repetitively during the consecutive hours to monitor delayed pneumothorax and pleural effusion.

Indication for the tissue collection and consecutive analysis of the individual results were discussed at the in-house multi-disciplinary panel. Patients data were de-identified, the informed consents for the

procedures were given by dedicated representatives after individual risk-based information. The retrospective analysis was approved by the ethics committee (No.2020 – 155) of the Martin Luther University Halle-Wittenberg.

Results

From July 2019 to August 2020 seven patients (four males, three females) with a median age of 68 (37;83) years suffering from unexplained ARDS received a transbronchial lung-cryobiopsy. Median number of days of ventilator dependency was 28 (17, 48). Patients' individual data are summarized anonymously in Table 1, more details are shown in supplemental material. One patient had a known mild emphysema, whilst the rest had no prior pulmonary disease. The distinct ARDS-cause was idiopathic (n = 3), infection with SARS-CoV-2 (n = 2), RSV pneumonia (n = 1) and bacterial pneumonia (n = 1). With intention to post-inflammatory ARDS all patients were effortlessly treated with systemic steroids before indication of the cryobiopsy was discussed.

Table 1
Patient and procedure details. Numbers are median or absolute count.

Median Age (years)	**68 (37;83)**
Male/Female	4/3
ECMO therapy	4
Median days on mechanical ventilation/ECMO before TBCB	28/18
Sufficient histopathology (n)	7/7
Impact on clinical management (n)	7/7
Biopsy location	LB5 n = 2 Left lower lobe n = 1 RB3 n = 1 RB8 n = 2 RB9 n = 1
Severe adverse event	Endobronchial bleeding n = 0 Hematothorax due to pleural defect in VATS n = 1 Hematothorax without pleural defect n = 1 Pneumothorax n = 0 Respiratory deterioration n = 0

ECMO: extracorporal membrane oxygenation; TBCB: transbronchial cryobiopsy; VATS: Video assisted thoracoscopy

At the time of TBCB no active infection was the main reason for the ARDS regarding to the serological, microbiological and laboratory testing. Bronchioalveolar lavage (BAL) was done in every patient at least two days prior to the biopsy and did not reveal any relevant bacterial load or immunological explanation. Extended laboratory testing excluded an underlying autoimmune disorder. Transbronchial forceps biopsy was earlier done in one patient without representative alveolar tissue.

Four patients were dependent on veno-venous ECMO support at the time of TBCB. The PTT-controlled heparinization was reduced in the periinterventional hours to a target of 50 seconds. Three patients did not depend on ECMO at the moment of bronchoscopy. None of the patients had an additional indication for therapeutic heparinization.

Biopsy locations were distributed equally between the right and the left lung. Five patients were biopsied with fluoroscopy, in two patients the transport to the endoscopy unit was impossible because patient transfer posed a relevant individual risk. All patients received three biopsies, and no intervention was impaired by immediate endobronchial bleeding after ZAVALA manoeuvre.

Histopathological evaluation revealed diagnostic material in all seven patients: Five diffuse alveolar damage (DAD, Fig. 2), one acute fibrinoid organizing pneumonia (AFOP) and one cryptogenic pneumonia (COP, Fig. 3) respectively. In two patients an individual therapeutic intervention based on the histological findings of AFOP and COP was initiated. In five cases the histology results with DAD offered no additional treatment opportunity but were important to guide the upcoming decisions regarding limitation of intensive care.

No pneumothorax occurred within the postinterventional period. In patient #1 increasing pleural fluid was detected with TUS, a pleural tube placement showed a hematothorax that needed a single surgical intervention (video assisted thoracoscopy). Here a pleural defect was identified as bleeding source. Red blood cell transfusion was necessary. Patient #4 experienced a delayed hematothorax with necessary thoracotomy 48 hours after TBCB. Diffuse pleural bleeding was described and treated with pleural packing, transfusion and correction of coagulation factors. However, complications occurred only in the two patients who were biopsied without fluoroscopy.

In the other five cases no severe complications occurred. Prophylactic blocking was easily placed and removed two days later. No severe endobronchial bleeding that might have caused additional maneuvers or earlier termination happened immediately during the TBCB.

Because of clinical deterioration due to medical conditions not related to TCBC none of the described patients survived the intensive care treatment. None of the patients deceased with direct correlation to the TBCB. On patient with SARS-CoV2-ARDS received a post-mortem examination that confirmed the histological diagnosis of COP gained by TBCB.

Discussion

Transbronchial cryobiopsy (TBCB) is feasible and of additional diagnostic benefit in patients that suffer from severe ARDS even during ECMO treatment. In our case series all TBCB revealed a sufficient histopathological characterization in patients suffering from unexplained ARDS.

TBCB was extensively analyzed especially in the diagnostic workflow of ILD. In this context it is broadly accepted that TBCB equally contributes to the final diagnosis when compared to surgical lung biopsy [6, 7]. Compared to surgical lung biopsy the lower rate of complications of TBCB and the comparable diagnostic yield is advantageous.

Recently TBCB has been reported in two retrospective series in a small number of patients with acute hypoxemic respiratory failure (AHRF) and ARDS without severe adverse events. However, these patients were investigated at a quite early moment after hospital admission, there is no information about the severity of the individual respiratory situation, especially need for mechanical ventilation [8, 9, 10].

In our patients we usually do not reach for tissue collection in an early ARDS, especially when no previous pulmonary pathology is known and usually an infectious cause might be assumed. In ARDS or AHRF tissue acquisition with open lung biopsy alone or in combination with BAL and lung forceps biopsy was reported to have a relevant impact to the diagnostic work up and change the treatment in up to 73% of the patients. It is however connected to a relevant number of severe adverse events and procedure related deaths [2]. In this particular patient cohort this is difficult to compare. Time to rapidly find an exact diagnosis is limited and usually does not allow several attempts of interventional methods. When tissue collection seems necessary the balance between a method with high diagnostic yield and expectable complication rate at the lowest possible level, TBCB should be considered, when surgical lung biopsy is not consented or not warranted for any reason and skills with TBCB are already established.

Because of the need for diagnostic precision on the one hand and manageable complications on the other hand, we decided not to perform TBFB regularly prior to TBCB. The TBFB prior to TBCB performed in one single patient did not reveal any relevant diagnostic information.

However, there is still debate on the procedural settings in TBCB [5]. Further studies have to contribute to this discussion. Transbronchial biopsy, even TBCB, has never been reported under ECMO. As this seems to be a situation with high clinical need, we could show that TBCB might be feasible with an acceptable risk profile. Also, open lung biopsy during ECMO treatment has never been reported before.

We acknowledge the relevant risk profile in our patients, but the side effects could be handled consecutively. However, complications need to be effectively monitored and treated, if necessary. Prophylaxis of endobronchial haemorrhage with inserted blocking utensils should be done especially when effective anticoagulation cannot be withdrawn. We did not work with a prophylactic balloon blockade, that is especially recommended during or immediately after TBCB when experience with the procedure is lacking or general endotracheal intubation is not performed [5]. However as “experience”

cannot be defined more specifically this should be decided by the individual operator. To avoid prolonged bleeding after the necessary post-procedural increase of heparinization we decided to regularly place Watanabe Spigots that are not linked to airway leakage as balloons and are easy to remove later on. As we experienced two severe complications in the patients where fluoroscopy was logistically impossible we postulate that this item should be mandatory to increase the periprocedural safety. When fluoroscopy is impossible to provide, TBCB especially in ARDS patients should not be performed.

Surveillance and treatment of procedure related side effects are essential. TUS has been reported to be an excellent tool for either exclusion of pneumothorax directly or delayed after a broad range of bronchoscopic interventions [11] or but also with exclusive focus on TBCB [12, 13], and is recommended to be used as first method for pneumothorax exclusion after procedures with increased risk for pneumothorax in the intensive care unit setting when compared to delayed chest X-ray [14]. In the one patient with pleural defect that absence of pneumothorax might be explained due to stiffness of the lung tissue but is not generalizable.

We scheduled the biopsies quite late in the patients' clinical course. The earlier cited studies reported performance of TBCB earlier in diagnostic workup / clinical course. This was however impossible in our patients since they were treated at later time of disease in our center. Whether an earlier transbronchial biopsy would have changed the clinical course remains speculation. This should be considered when even the initial presentation cannot be explained by infection or other common causes of ARDS. We used TBCB to evaluate the prognosis of the pulmonary damage. The suggested and reasonable diagnostic workflow describes tissue collection when previous steps including BAL could not illuminate the cause of the unexplained ARDS [1]. But it is reasonable that the earliest possible chance to secure the diagnosis and get an idea of the patients' prognosis will help in difficult therapeutic decisions and canalize limited ICU resources.

Limitations of this report are due to the small number of patients and the missing control group. Results are not generalizable, prospective clinical studies should be scheduled to increase knowledge about the value of TBCB in this group of patients with enormous clinical need for the right decision.

Conclusion

Transbronchial cryobiopsy (TBCB) is feasible and of additional diagnostic value in patients that suffer from ARDS and even under ECMO support. It should be taken into consideration in unexplained and non-resolving ARDS. When following the general recommendations for TBCB and ensuring close post-interventional monitoring, side effects and complications might be acceptable and manageable.

Abbreviations

AFOP – Acute fibrinoid organizing pneumonia

AHRF – Acute hypoxemic respiratory failure

ARDS – Acute Respiratory Distress Syndrome

BAL – Bronchoalveolar Lavage

COVID – Corona Virus Disease

COP – cryptogenic organizing pneumonia

DAD – Diffuse alveolar damage

ECMO – Extracorporal membrane oxygenation

HR-CT – High resoluted computed tomography

ILD – Interstitial Lung Disease

SARS – Severe adult respiratory syndrome

TBCB – Transbronchial cryobiopsy

TBFB – Transbronchial forceps biopsy

Declarations

Statement of ethics:

This study was performed in accordance with the World Medical Associations Declaration of Helsinki. Patients' guardians have given their written informed consent and the study was approved as retrospective analyzation by the IRB (2020-155).

Involvement of animals: Not applicable.

Consent for publication: Not applicable

Conflict of Interest Statement:

All authors have no possible conflicts of interests to declare.

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Author contributions:

Directly provided patient care: All authors

Analyzation of data: All authors

Drafted, edited manuscript and images: All authors

Manuscript revision: All authors

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Figures

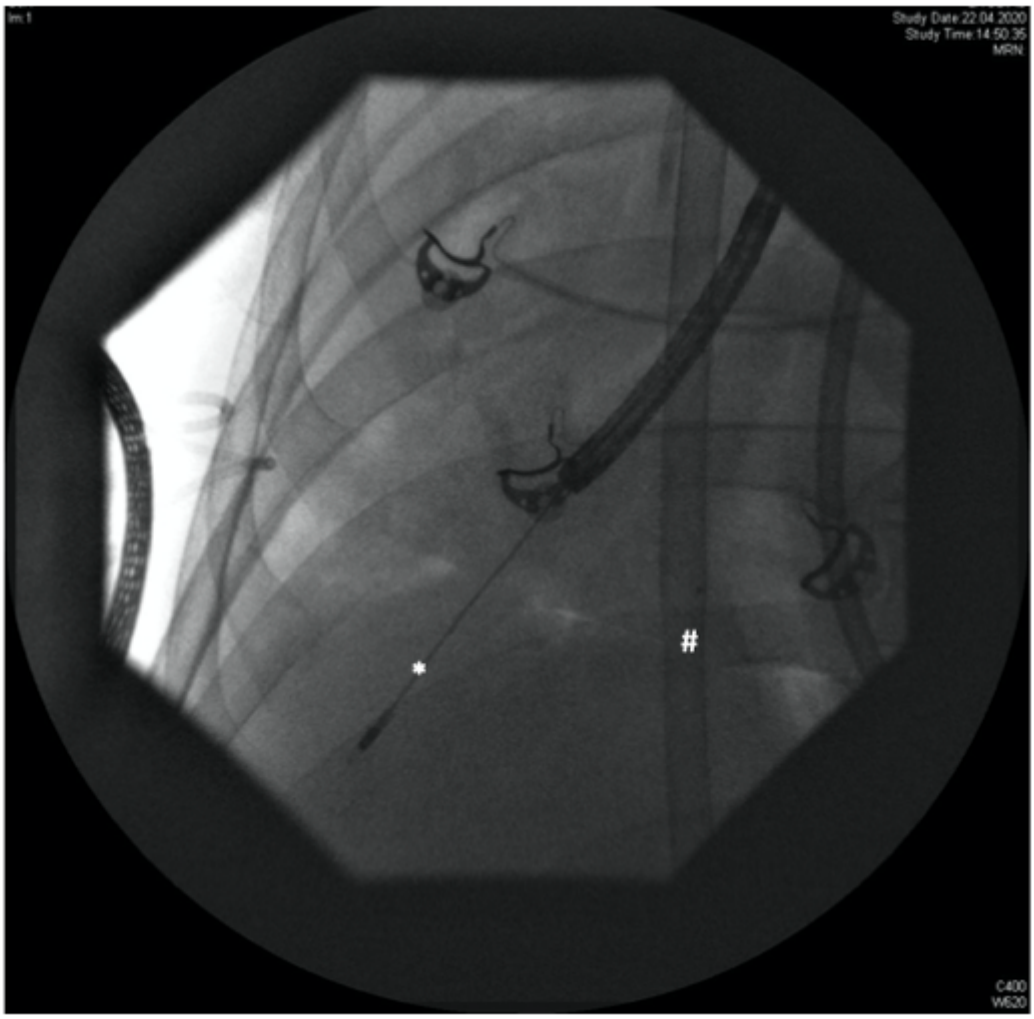

Figure 1

Transbronchial cryobiopsy (1.9 mm flexible cryoprobe, ERBE, Tuebingen, Germany, *) in the right lower lobe. ECMO cannula located in the inferior cava vein (#)

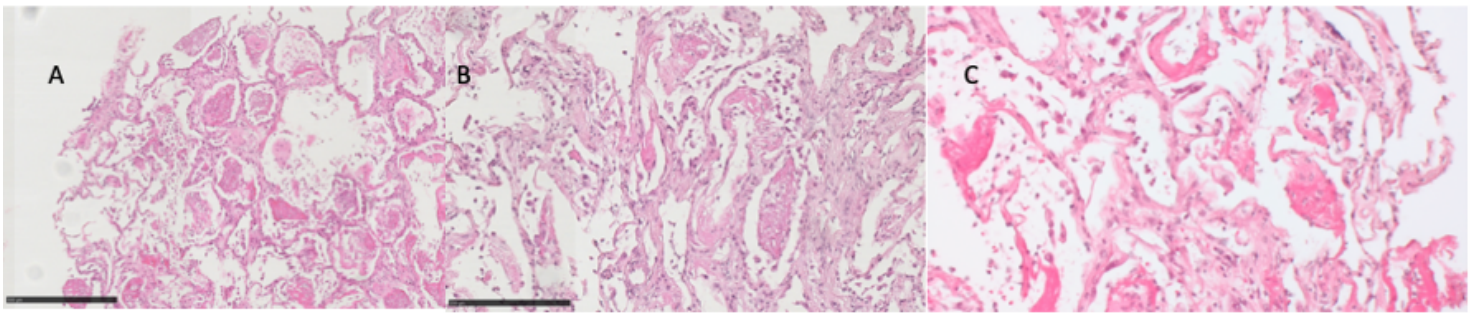

Figure 2

Diffuse alveolar damage - Hamman Rich Syndrome (A: 80x; B: 170x; C: 200x).

A: Initial formation of airspace granulation tissue plugs in alveolar ducts

B: Accumulation of intra-alveolar macrophages

C: Organizing /proliferative phase AIP

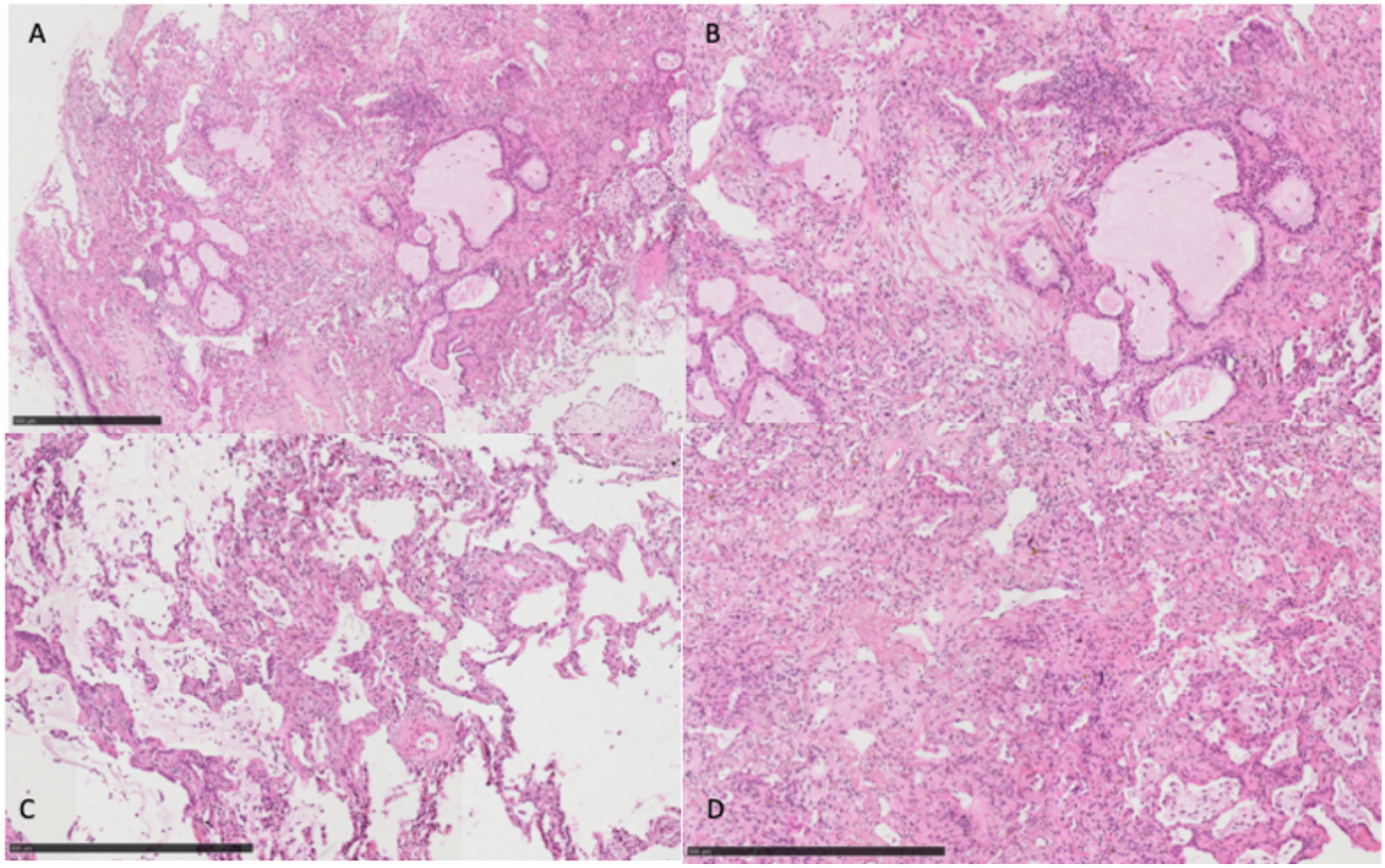

Figure 3

COVID-ARDS (A: 70x, B: 100 x, C&D: 120x)

A&B: Fibrotic lung parenchyma with mucous metaplasia, chronic interstitial inflammation and centered myofibroblastic proliferations

C: Fibrotic parenchyma with intraalveolar edema

D: Fibrotic parenchyma with chronic interstitial inflammation and accumulated macrophages