증례 5

랫드의 간질성 폐염

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1. 질병명 : Interstitial pneumonia

2. 본질명의 개요 역사 및 역학

○ Michael R Elwell, Joel F Mahler, G N Rao:
"Have You Seen This?" ; Inflammatory Lesions in the Lungs of Rats. Toxicologic Pathology, 25: 529-531, 1997.

- o Male and female F344 rats, approximately 19 weeks old, from prechronic toxicity studies performed for NTP/NIEHS over a period of several years at different laboraories located throughout the US.
- o The rats were supplied by 2 different production colonies located in the eastern and western areas of the US.
- o Gross findings
  - In some rats the lesions were noted as pale or tan foci in the lungs
- o Microscopic findings
  - A prominent increase in perivascular lymphocytes
  - A variable increase in the amount of peribronchiolar lymphoid tissues
  - Frequently an inflammatory cell exudate within the alveolar spaces
  - Focal hyperplasia of alveolar type 2 cells
- o Similar lung lesions were not observed in B6C3F1 mice concurrently on study with affected rats.
- o Similar lung lesions were not observed in F344 rats at the end of 2-year NTP studies.
- o Virus, mycoplasma, bacterial serology, bacterial culture, protozoal identificaltion: negative
- o EM:
  - No virus particles were identified.
  - Rod shaped bacteria were observed in the alveolar spaces.
  - Bacteria were not observed in the bronchi/ bronchioles of rats with alveolar organism.

○ Craig L Franklin, Cynthia L Besch-Williford, Robert J. Russell: *Research Update:* Idiopathic Lung Lesions in Rats. ACLAD NEWSLETTER, 1998.

- o SD rats, male and female
- o Groups of five rats at 2, 6, 8, 10, 12 and 18 weeks of age
- o Asymptomatic
- o Gross lesions
  - • Seen in 8-, 10-, 12-, and 18-week-old rats
  - • Small, gray to white, raised, multifocal, and randomly distributed on all lung lobes
- o Microscopic lesions
  - • 2-week-old rats: no lesions
  - • 6-week-old rats: mild multifocal perivascular lymphoid infiltrates
  - • 8-week-old rats: More severe, multiple perivascular lesions
  - • 10 to 12-week-old rats: Most severe
    - * Multifocal perivascular lesions often accompanied by foci of interstitial pneumonia
    - * Localized consolidation of the lung
  - • 18-week old rats:
    - * Fewer lesions were seen
    - * Aveolar septal thickening with associated luminal macrophage infiltrates with minimal consolidation
  - • Collectively, lesions were suggested to be resolving
- o The prevalence of the disease is sporadic.
- o No difference in lesion severity or number between males and females
- o The disease occurs in a wide variety of rat strains/ stocks.
- o Etiology
  - • Foreign bodies, bacteria, fungi were ruled out.
  - • A virus was cultured from the lung of affected rats as the putative etiologic agent.
- o Experimental infection studies with this virus are currently underway.

○ M. Slaoui, H. C. Dreef and E. van Esch: Inflammatory Lesions in the Lungs of Wistar Rats. Toxicologic Pathology, 26: 712-713, 1998.

- o Wistar rats used in toxicology studies, male and female
- o 2, 4, 13 and 24 weeks toxicity studies
- o Microscopic lesions
  - • An increase in perivascular mononuclear cells (mainly lymphocytes) localized around the medium-sized arteries throughout the lungs and extending to the peribronchiolar areas.

- A tendency toward an increase in bronchus associated lymphoid tissue (BALT)
- Focal infiltrates of mixed inflammatory cells
  (macrophages, lymphocytes, and occasionally neutrophils)
  in the interstitium and in alveolar spaces.
- In more severe cases, focal hyperplasia of alveolar type II cells

o The incidence of the lesions
- Over the last 3 years, up to 50% in 2 and 4 week toxicity studies.
- The incidence and the severity of the lesions tended to diminish in 13 and 26 week toxicity studies.
- The finding could not be detected in 1 year toxicity studies.

o Etiology
- The supplier guarantees each rat to free of viral, bacterial, mycoplasmal, and fungal infectious agents and parasites as recommended by FELASA (Federation of Laboratory Animal Science Association).
- Free of mouse adeno virus, lymphocytic choriomeningitis virus, MVM, and rotavirus.

o Animals seem to acquire immunity with time.

○ A letter from Charles River Laboratories to Customer and Colleague. 1999.

o Starting September 1998, rats from 170 worldwide Charles River colonies

o Tested by Charles River Diagnostic laboratories in Wilmington, Massachusettes.

o Over 2000 rats were necropsied.

o Only 6 rat production rooms exhibited lesions compatible with this syndrome.

o Charles River facilities in Germany and France

o Actions by Charles River
- Meetings of pathologists were held to characterize the lesion
- Continue to monitor Charles River areas for this lesion
- Funding academic R&D programs to pursue the etiology of this disease o Rat Respiratory Virus(RRV)
- 1992: Sporadic unpublished reports
- 1997: The first published description
- Investigatons of a potential etiologic agent have been underway
- The name of the first commercial supplier in whose rats it was noted or Rat Respiratory Virus(RRV) was proposed.
- Not likely to contaminate the environment

(Transmission probably requires animal-to-animal exposure)

- o Gross findings
  - Only rarely visible
  - Gray to tan foci scattered across the pleural surface of the lung
- o Microscopic findings
  - Prominent and characteristic lymphoid cuffing of peripheral vessels
  - Brochioles and adjacent alveoli: Occasionally contain syncytial cells, macrophages, lymphocytes and neutrophils, type II epithelial hyperplasia
  - Minimal to moderate in severity
- o No sex predilection
- o Lesions are most severe at 8-10 weeks of age and resolve with time
- o Multiple strains of rats are susceptible
- o Etiology
  - The agent has not been definitively identified.
  - The agent pass bacteriologic filters and can be propagated in tissue culture.
- o The only mechanism of screening for the agent is histology using animals 8-16 weeks of age from the endemically infected groups.

3. 재료 및 방법 :

○ SD rats, 9 weeks old, 10 animals

○ H&E stain

○ Light microscopic examination of the lungs

4. 원인 : Caused by unidentified agent (possibly virus)

5. 간략한 임상증상 : No sign

6. 육안소견 :

- Incidence: 2/10 (20%)
- Only rarely visible
- Gray to tan foci scattered across the pleural surface of the lung

7. 조직병리소견 :

- Incidence: 5/10 (50%)

- A prominent increase in perivascular lymphocytes
- A variable increase in the amount of peribronchiolar lymphoid tissues
- Frequently an inflammatory cell exudate within the alveolar spaces
- Focal hyperplasia of alveolar type 2 cells
- Thickening of alveolar walls due to infiltration of inflammatory cells, mainly mononuclear cells
- Multifocal granulomatous aveolitis

8. **진단** : By histopathological examination
(No other diagnosis is available so far)

9. **감별진단** : 형태학적으로 볼 때, 원인은 아직 밝혀지지 않았지만, 간질성폐염을 일으킬 수 있는 모든 원인들 중에서 바이러스로 인한 간질성 폐염을 비교·검토해야 한다.

폐염의 형태학적 분류

○ Bronchopneumonia
○ Lobar pneumonia
○ Interstitial pneumonia
○ Bronchointerstitial pneumonia
○ Abscesses of the lung and embolic pbeumonia

특별한 형태의 폐염

○ Gangrenous pneumonia
○ Aspiration pneumonia
○ Lipid pneumonia
○ Uremic pneumonia
○ Granulomatous pneumonia
○ Alveolar filling disorders

동물의 간질성폐염 원인

○ 감염: 바이러스, 세균, 진균, 기생충
○ 흡입된 화학물질: 산소(>50%), 연기 등
○ 섭취한 독소 또는 그 전구물질: L-tryptophan, perilla mint ketone, furanoterpenoid, paraquat and kerosene 등

○ 약품의 부작용

○ 과민반응: allergens

○ 내인성 대사 / 독성 조건: Uremia, shock, DIC 등

○ 방사선 조사

○ 기타

랫드에서 감염으로 인한 폐염

○ DNA 바이러스 감염

- 폭스바이러스 감염(Poxviral Infection)

○ RNA 바이러스 감염

- 파커 랫드 코로나바이러스(Parker's rat coronavirus: PRC)
- 마우스 폐렴 바이러스(Pneumonia Virus of Mice : PVM)
- 센다이 바이러스(Sendai virus)

○ 그람음성 세균성 감염

- 기관지 패혈증균 감염(*Bordetella bronchiseptica* Infection)
- 섬모 연관 호흡기 간균 감염(Cilia-associated Respiratory (CAR) Bacillus Infection)
- 설치류 호흡기 마이코플라즈마 감염(Murine Respiratory Mycoplasmosis: MRM)
- 파스퇴렐라 뉴모트로피카 감염(*Pasteurella pneumotropica* Infection)

○ 그람양성 세균성 감염

- 코리네박테륨 쿠체리 감염*(Corynebacterium kutscheri* Infection)
- 연쇄상구균 감염
- 슈도모나스증(Pseudomonas aeruginosa Infection: Pseudomoniasis)

○ 진균 감염(MYCOTIC INFECTIONS)

- 뉴모시스티스 카리니 감염(*Pneumocystis carinii* Infection).

랫드의 감염으로 인한 간질성 폐염

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○ 진균 감염

- 뉴모시스티스 카리니 감염(*Pneumocystis carinii* Infection).

폭스바이러스 감염(Poxviral Infection)

○ 임상소견
  ㅇ 잠복감염에서부터 높은 폐사율을 보이는 피부 마마(pox)나 꼬리절단까지 다양함.
  ㅇ 피부(dermal)와 호흡기도(respiratory tract)에 병변이 있음.
○ 현미경적 소견
  ㅇ 간질성폐염: 부종, 출혈, 흉막 삼출액(pleural effusion)을 동반함.
  ㅇ 상부 호흡기도: 국소성 염증 병변

파커 랫드 코로나바이러스(Parker's rat coronavirus: PRC)

○ PRC의 비강내(intranasal) 접종
  ㅇ 비염(rhinitis), 기도염(tracheitis), 간질성 폐렴(interstitial pneumonitis)
  ㅇ 새끼에서 국소성 무기폐(focal atelectasis) 및 많은 폐사가 일어난다.
  ㅇ 타액선이나 누선의 병변

마우스 폐렴 바이러스(Pneumonia Virus of Mice : PVM)

○ 호흡기도에 친화성이 있는 *Pneumovirus* 속에 속하는 파라믹소바이러스
○ 마우스, 랫드, 햄스터와 아마도 기니픽과 져빌(gerbil)을 감염
○ 병리
  ㅇ 간질성 폐렴(interstitial pneumonitis): 급성단계의 전형적 병변, 혈관염(vasculitis)과 괴사를 동반
  ㅇ 기관지관련 림프조직(BALT)의 과형성(hyperplasia)
  ㅇ 혈관주위염(perivasculitis)
  ㅇ 다소성 간질성 폐렴(multifocal intersitial pneumonitis)등을 동반한 현저한 혈관주위 침윤(perivascular infiltrates)이 나타남.

센다이 바이러스(Sendai virus)

○ 파라인플루엔자 1, Paramyxoviridae과의 RNA 바이러스
○ 마우스에게 고유하지만(indigenous), 실험실 랫드와 햄스터에게도 호흡기질병
○ 랫드에서 센다이 바이러스 감염의 병인론(pathogenesis)은 유전적으로 저항성이 있는 마우스 계통에서의 센다이 바이러스와 유사함.
○ 조직병리학
  ㅇ 급성단계
    • 비염: 호흡기 상피세포에 국소성(focal)에서 미만성(diffuse) 괴사
    • 하부 호흡기도에서는 다핵융합체 상피세포를 동반한 다소성 과형성 내지 농양성 기관지염과 세기관지염 심한 경우에는 괴사성 세기관지염이, 그리고 자주 국소성 폐포염 폐포 중격은

과세포성을 나타내고 침윤된 세포는 폐포 대식세포(alveolar macrophage), 호중구, 림프구들

- 바이러스 증식: Type I, II pneumocytes, alveolar macrophages

o 아급성(subacute)단계나 회복단계

- 림프구나 형질세포로 구성된 혈관주위(perivascular)와 기관지주위의 둘러쌈 (peribronchial cuffing)이 현저함.
- 단핵세포 침윤은 폐포 중격에 수주 동안 존속함
- 잔존한 간질성 섬유증이 폐포벽에 남아있을 수 있음.

뉴모시스티스 카리니 감염(*Pneumocystis carinii* Infection).

○ 세계적으로 분포하고 있는 비정형의 곰팡이인 *P. carinii*는 면역이 약화된 사람의 경우, 특히, AIDS 환자에 있어서 질병과 치사의 중요한 원인으로 인식됨.

○ 재래 랫드의 많은 콜로니들이 *P. carinii*에 자연적으로 감염되는 것 같고, 실험실 랫드 그리고 때로 토끼가 이 곰팡이를 보유하고 있다는 증거가 있음.

○ 뉴모시스티스증(pneumocystosis)는 고양이, 말, 개, 원숭이 등의 동물에서 발생함.

○ 육안적 소견

o 폐: 미만성 내지 국소성 경결, 심하게 허탈하고 불투명한 옅은 분홍색을 자주 나타냄.

○ 현미경 소견

o 폐포는 벌집 모양을 나타내는 거품 모양의 호산성 물질로 가득 참.

o 무흉선 랫드에 있어서 폐 병변: 폐포 대식세포가 산재하는 경미한 간질성 폐염에서부터 폐포가 전형적인 거품물질로 확장되어 있는 심한 간질성 폐염까지 다양함.

o 보다 더 진전된 경우: 침윤한 염증세포와 거품 모양의 폐포 삼출물 외에도 II형 폐포세포의 현저한 증식과 간질성 섬유화(interstitial fibrosis)가 나타남.

o 고모리의 methenamine 은염색법을 이용하여 염색한 조직에 있어서 많은 수의 검은 영양체(trophozoites)와 직경이 3~5 μm인 효모양의 낭포가 폐포 내에 홀로 또는 군집을 이루어 나타남.

o 전자현미경 관찰: filapodia가 있는 영양형이 I형 폐포세포와 근접하여 나타남.

o 폐 압흔 도말표본(impression smear), Giemsa염색: 낭포내 소체(핵)가 관찰됨.

10. 치료 및 예방대책 : 치료와 예방대책은 아직 없음.

11. 참고문헌

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