



吉林大学

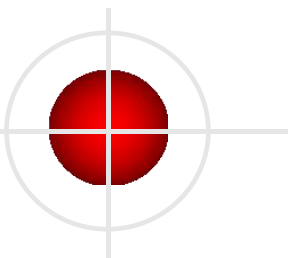


# 从病理学角度谈动物疾病诊断

高 丰

分子与免疫病理学教授/博士生导师

E-mail: [gaofeng@jlu.edu.cn](mailto:gaofeng@jlu.edu.cn)



在人满为患的医院里，有这么一群神秘的医生：他们几乎不跟病人交流，却最终决定着病人的肿块要不要切、切多少，该用什么靶向药治疗最好。

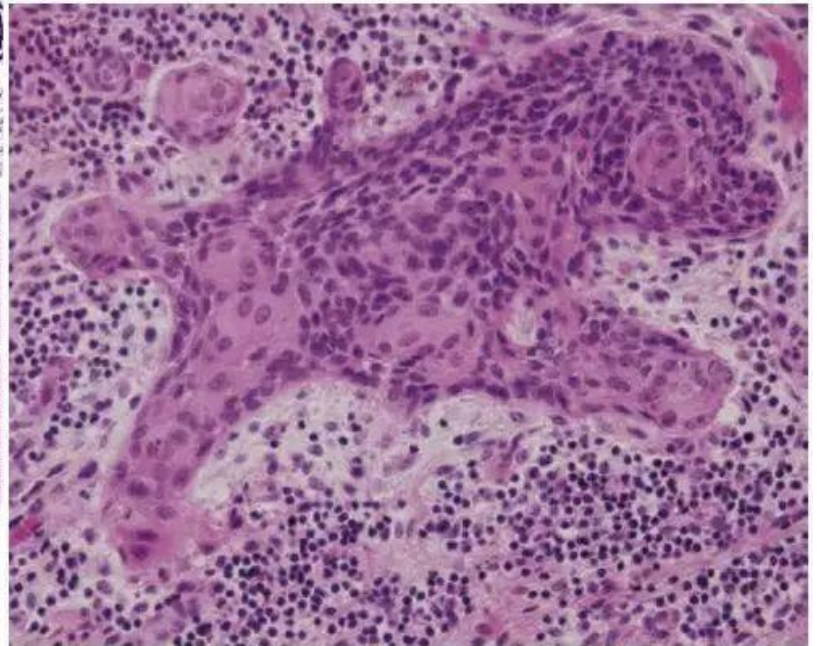
他们像手艺精湛的匠人，每天用刀子、剪子、镊子、尺子，把送到他们面前的“人肉”切成厚度只有几毫米的小块儿。

他们还像细致的料理师，会用到烘箱、染料、专门的切片机，经过几十道工序把那几毫米的小肉块儿处理成只有几微米厚的薄片。

他们更像火眼金睛的侦探，根据显微镜下那个小小光圈里的影像，判断出病变组织是炎性病变还是肿瘤，是良性还是恶性，作出被称为“金标准”的诊断，保证病人不会被过度治疗也不会治疗不足。



乳腺纤维腺瘤和良性前列腺增生患者样本的组织病理学图像  
(Ma, Ivy Clement)



外阴浸润性鳞癌的病理图像  
(Bellevue Hospital- Khush Mittal和 Deline Da Costa)

**这群神秘的医生就是被称作“医生的医生”、隐藏在幕后的病理医生！**

## 诊断病理学家：

尸体剖检可为临床医师提供如何控制疾病暴发和如何改善动物管理等方面的重要信息。

## 外科病理学家：

对活体动物取得的组织（活体组织检查）进行检测，可指导临床医生诊断疾病。

## 毒理病理学家：

通过实验动物检测和评估药物及化学物质的效果和安全性。

## 临床病理学家：

检测血液、血清和血清化学物质和细胞，可为临床医生提供详细的信息。

## 实验病理学家：

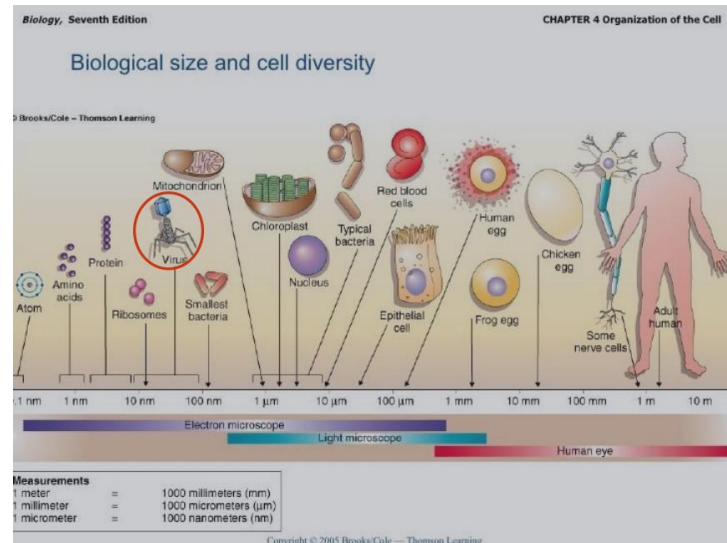
研究人类和动物疾病组织、细胞和发病机理。



# 疾病的诊断方法

- 病史、症状及病理学检查 (大体剖检、病理组织学观察)
- 病原、免疫学及分子生物学检查
- 病理学检查
  - 特殊病理学检查
    - 组织化学染色 (Histochemistry): Acid-fast染抗酸菌
    - 免疫组织化学染色 (Immunohistochemistry, IHC): 检测病原出现位置
    - 原位杂交 (In situ hybridization): 检测病原核酸
    - 聚合酶链反应 (PCR): 检测少量病原核酸
    - 电子显微镜检查

病理学在疾病诊断方面扮演的角色



# 案例一

## 柯萨奇B3病毒感染所致川金丝猴死亡病例



2005年9月，长春市某动物园送检1只5岁雌性金丝猴死亡病例，出现呼吸促迫，咳嗽，饮水和食欲减退，不愿活动等临床症状，用吹管给药，投注1支头孢拉啶(0.5g/支)和1支地塞米松(1mL/支)。20min后，金丝猴出现口吐白沫，抽搐现象，病程持续8h左右死亡。

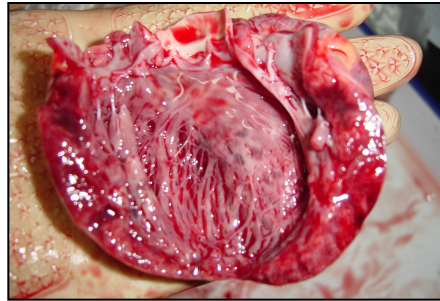
Journal of  
Virology

**Complete Genome Sequence of a  
Coxsackievirus B3 Isolated from a Sichuan  
Snub-Nosed Monkey**

Wenqi He, Huijun Lu, Kui Zhao, Deguang Song, Xianying Gai and Feng Gao  
*J. Virol.* 2012, 86(23):13134. DOI: 10.1128/JVI.02365-12.



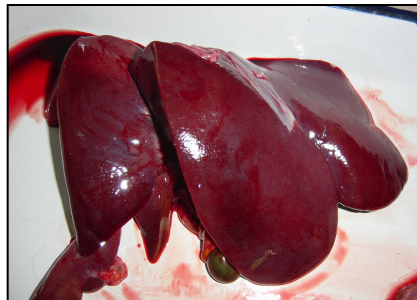
心外膜出血、心肌坏死



心内膜出血



肺膨胀、淤血



肝脏肿大



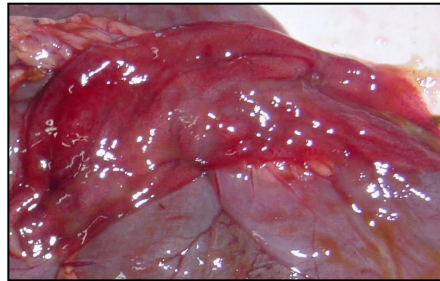
肾脏肿大



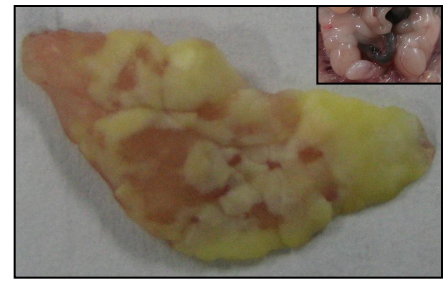
肾盂出血



脾脏肿大

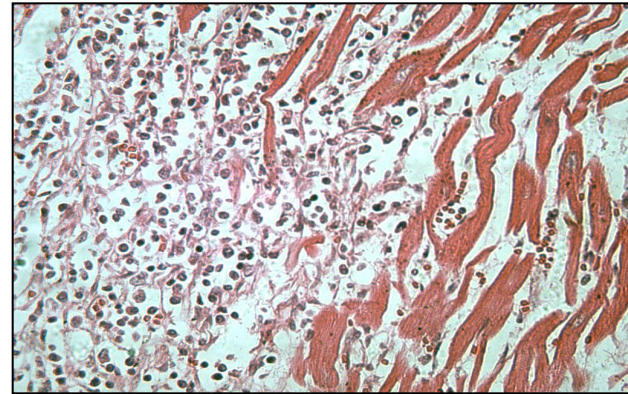
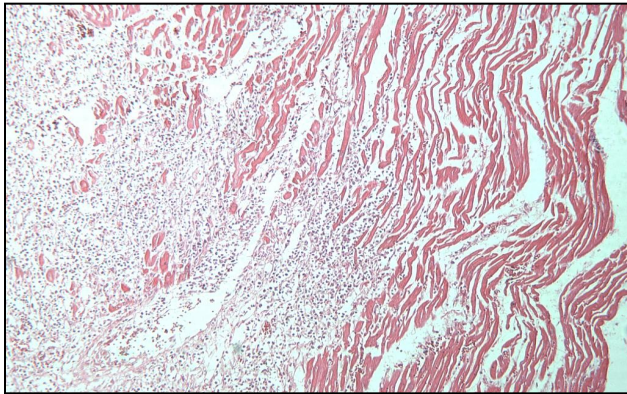


卡他性肠炎

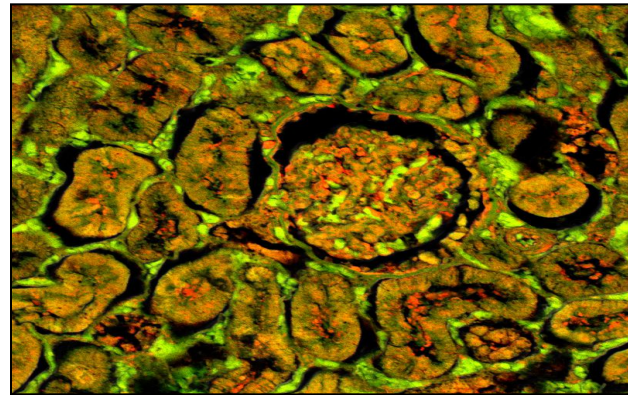
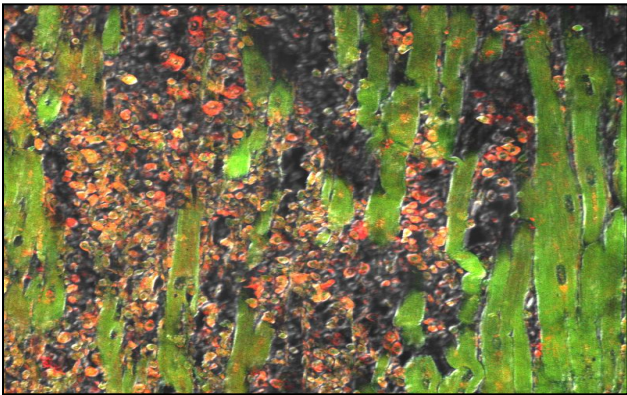


脂肪坏死

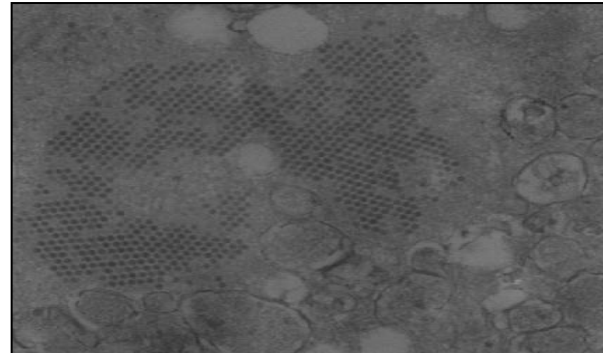




部分心肌纤维崩解、断裂，肌纤维间有炎性细胞浸润（H&E染色）



免疫荧光染色可见淋巴细胞浸润



电镜负染观察可见直径20~25nm，形似小RNA病毒的粒子

## 案例二

### 一起高致死性皮肤型鸡痘案例

2009年12月，北京家禽育种有限公司吉林正大褐肉鸡饲养场内大规模暴发鸡痘，约有1万只肉鸡发生死亡。据该场技术员描述，在肉鸡28日龄时，气雾免疫；在35~38日龄时，将颗粒料更换为粉料；在42日龄时，接种新城疫疫苗；之后，46日龄时，约有10000只鸡发病，发病鸡口腔糜烂，在口腔、背、肛门、翅膀下等无毛、少毛部位可见有大面积痘疹。一周后，该场所饲养的10000多只鸡全部死亡。

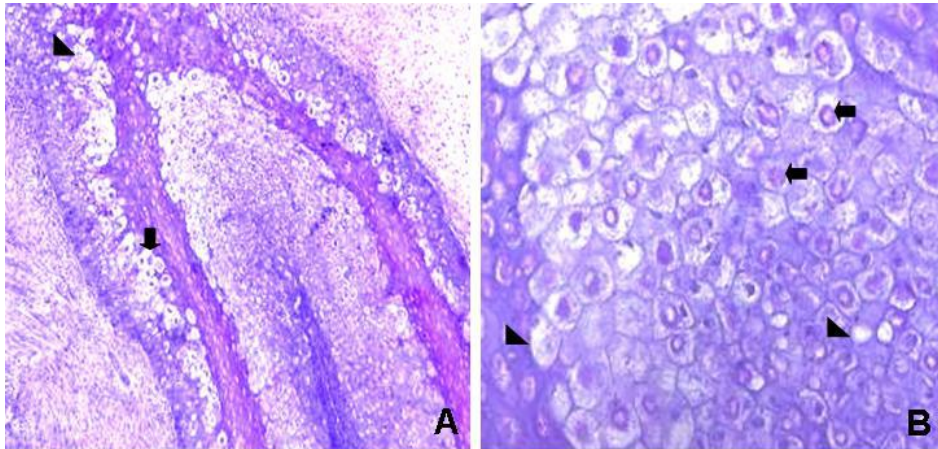




# 高致病性FWPV感染病理变化



无毛或少毛部位可见大面积痘疹



皮肤棘细胞胞浆内可见典型的嗜酸性病毒包涵体

DISPATCHES

## Highly Pathogenic Fowlpox Virus in Cutaneously Infected Chickens, China

Kui Zhao,<sup>1</sup> Wenqi He,<sup>1</sup> Shengnan Xie,<sup>1</sup> Deguang Song, Huijun Lu, Wei Pan, Ping Zhou, Wenfeng Liu, Rongguang Lu, Jiyong Zhou, and Feng Gao

We investigated an acute outbreak of the cutaneous form of fowlpox among chickens in China in November 2009. Using pathologic and virologic methods, we identified a novel type of fowlpox virus that carried an integrated genomic sequence of reticuloendotheliosis virus. This highly pathogenic virus could lead to severe ecologic effects and economic losses.

Fowlpox has been reported worldwide as a mild to severe poultry disease (1). Caused by fowlpox virus (FWPV), the disease is primarily found in 2 forms, cutaneous and diphtheritic (2). The cutaneous form is usually mild and characterized by multifocal cutaneous lesions on unfeathered areas of the skin. The more severe diphtheritic form is characterized by fibrous necrotic proliferative lesions on the mucous membranes of the respiratory and gastrointestinal tracts and causes more deaths than the cutaneous form, usually resulting from asphyxiation.

In recent years, fowlpox outbreaks in poultry flocks have been gradually increasing because of an emerging novel type of FWPV (3–5). The pathogenic traits of this virus type are likely enhanced by integrated reticuloendotheliosis virus (REV) sequences of various lengths in the FWPV genome (6–8). Although this variant FWPV has been found widely (7,9–14), the reported illness and death rates from the cutaneous form of fowlpox in chickens have not reached 100%. We investigated a severe outbreak of cutaneous fowlpox in a poultry flock in northeastern China in which all infected chickens died. The flock had not been vaccinated with an FWPV vaccine.

### The Study

In November 2009, a natural outbreak of the cutaneous form of fowlpox occurred in a poultry flock in Jilin Province in northeastern China (125°35' E, 43°88' N). A total of 10,000 brown breeding, 46-day-old chickens (Jilin Zhengda Co., Ltd, Changchun, China) used for egg production were affected. The flock had not received vaccination against FWPV.

DOI: <http://dx.doi.org/10.3201/eid2007.131118>

Province in northeastern China (125°35' E, 43°88' N). A total of 10,000 brown breeding, 46-day-old chickens (Jilin Zhengda Co., Ltd, Changchun, China) used for egg production were affected. The flock had not received vaccination against FWPV.

Clinical signs, including listlessness, anorexia, and typical skin pock lesions, were observed in all infected chickens. Lesions types varied in size and type: ulcerated, multifocal, or coalescing proliferative cutaneous exanthema variolosum. The lesions appeared on the skin in unfeathered areas of the backs, the eyelids, and the wings (Figure 1). All of the birds died within 10 days after clinical signs first appeared.

Postmortem examinations were performed for pathologic evaluation. Samples submitted for histopathologic examination included skin from the varioliform exanthema areas, trachea, thymus gland, bursa of Fabricius, and internal organs. Microscopic examination of skin lesions showed swelling, vacuolation, and characteristic eosinophilic cytoplasmic inclusion bodies in the stratified squamous epithelial cells of the follicular pili (online Technical Appendix Figure 1, <http://wwwnc.cdc.gov/EID/article/20/7/13-1118-Techapp1.pdf>). No obvious lesions were observed in other organs.

Electron microscopy of the clarified supernatant of the scab specimens collected from the skin of infected chickens showed characteristic FWPV virions, which have an ovoid shape (online Technical Appendix Figure 1). We attempted to isolate the virus by injecting the chorioallantoic membranes (CAM) and allantoic cavities of 9-day-old specific pathogen free (SPF) chicken embryos with the scab specimens that were positive for FWPV. White, raised variolles were observed on the CAMs of the embryos 4 days after injection (online Technical Appendix Figure 1). Electron microscopy also showed FWPV-shaped virions in the supernatant of the CAMs. After 5 blind passages at 4-day intervals, no other viruses were isolated from the allantoic cavities of the SPF chicken embryos.

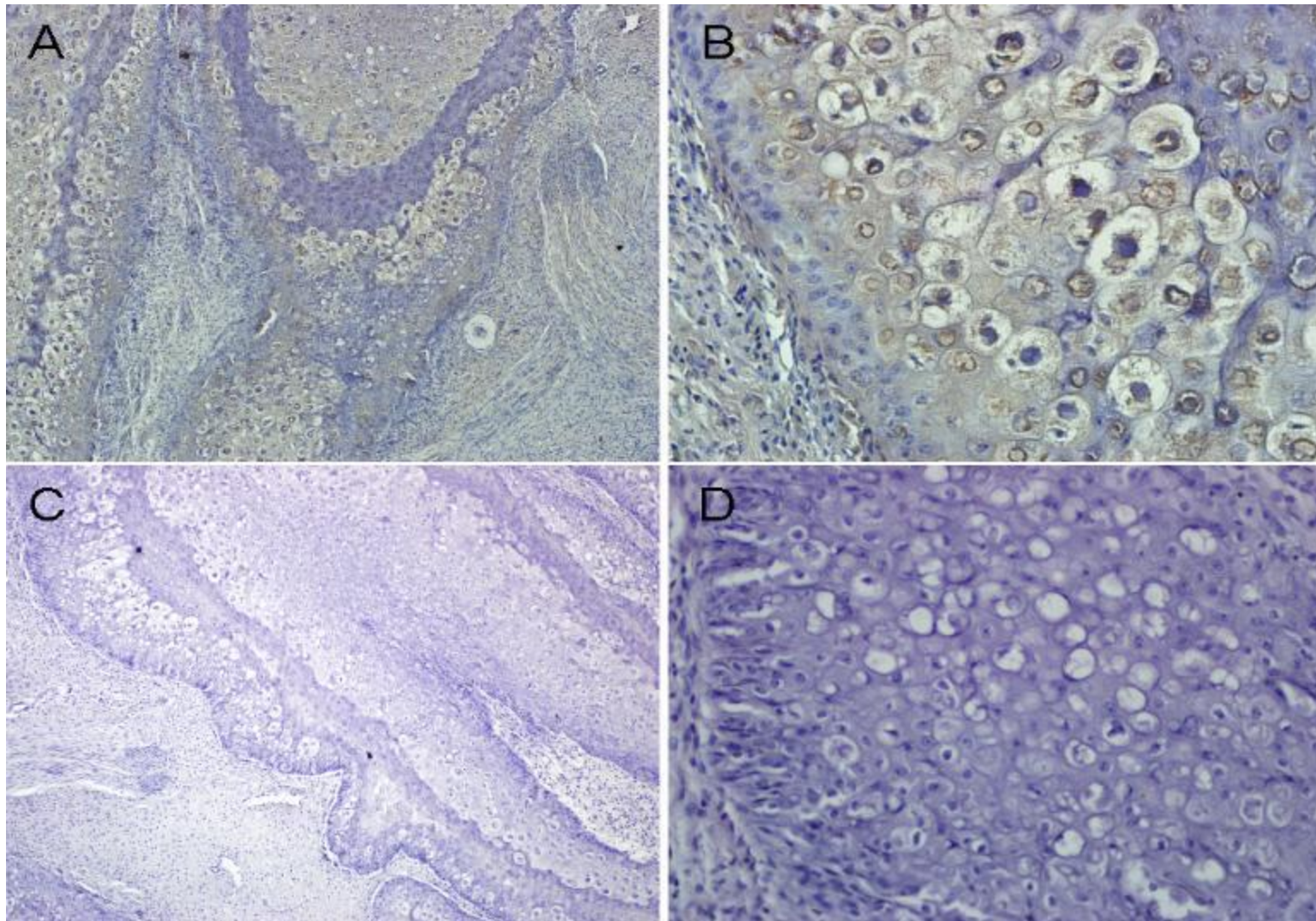
We used indirect immunofluorescence and a DF-1 chicken embryo fibroblast cell line to test the ability of the FWPV isolate from the CAMs to invade cells in vitro. Chicken anti-FWPV polyclonal antibody was used as the primary antibody; the secondary antibody was fluorescein isothiocyanate-conjugated goat anti-chicken IgG. Cellular nuclei were stained by using 4',6-diamidino-2-phenylindole. In some cells, typical bright, DNA-containing poxvirus factories were evident, often coincident with virus antigen-specific green fluorescence, at 3 days postinfection (dpi) (online Technical Appendix Figure 1).

Viral genomic DNA was extracted from scab specimens, and PCR amplification was performed immediately by using the specific primers for FWPV P4b gene (P4b

<sup>†</sup>These authors contributed equally to this article.



## 免疫组织化学 (IHC) 检测



(A, B) 感染病鸡皮肤的IHC检测; (C, D) 正常鸡皮肤。



# 案例三

## 吉林长春周边猪场发生疑似PHEV感染案例



流感型  
(influenza-like, ILI)



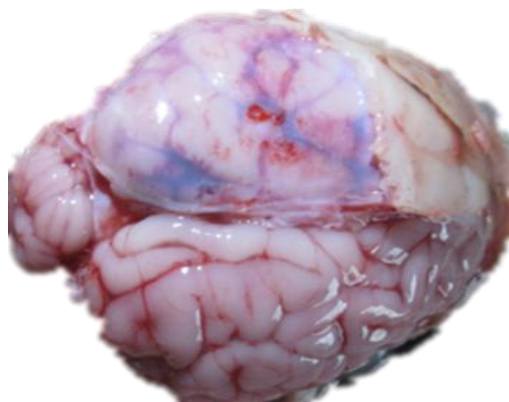
脑脊髓炎型  
( Encephalomyelitis )



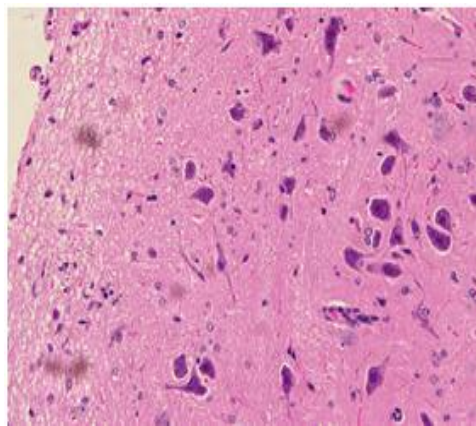
呕吐衰竭型  
( Vomiting and Wasting, VWD )



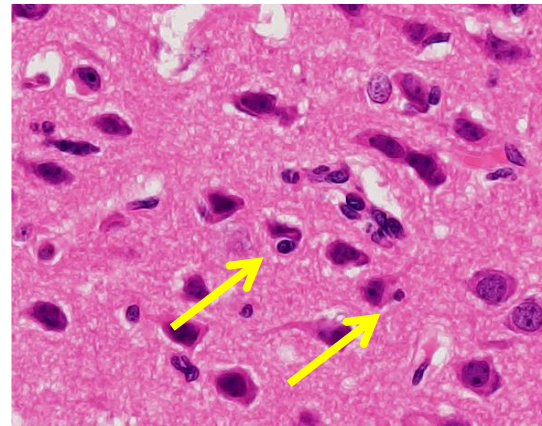
# 猪血凝性脑脊髓炎病理变化



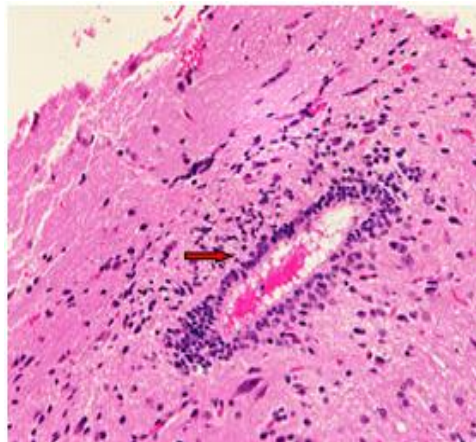
脑膜淤血



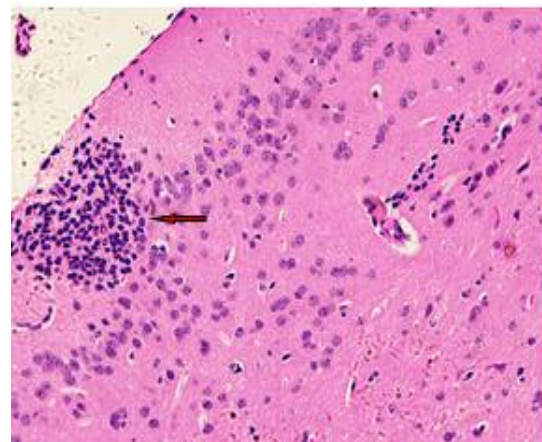
神经元变性坏死



噬神经现象

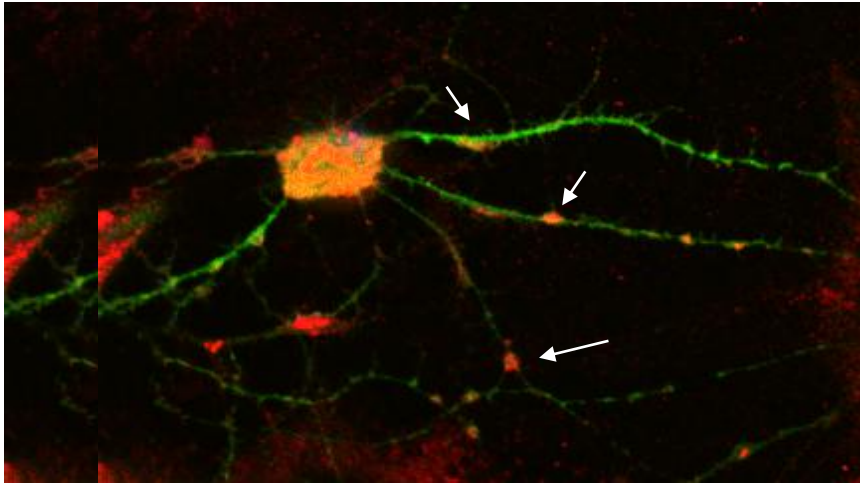


“血管套”



“胶质细胞结节”

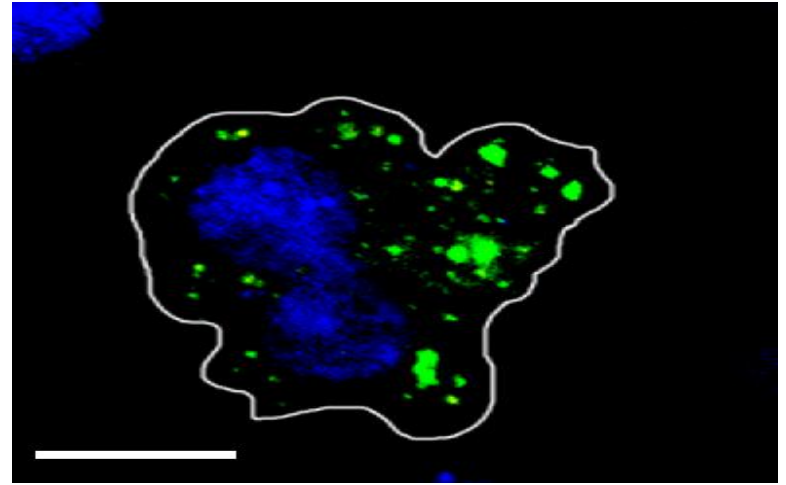




原代大脑皮质神经元感染模型

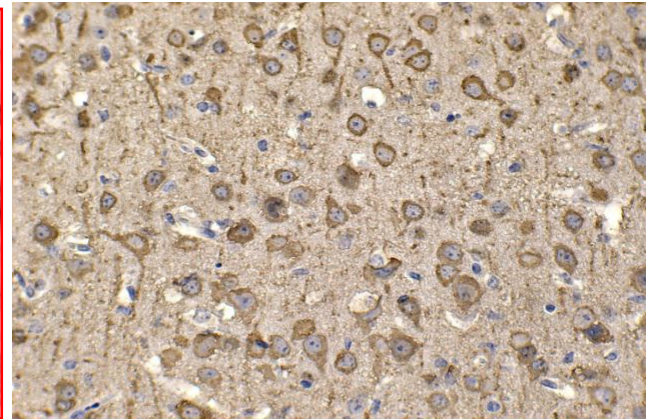
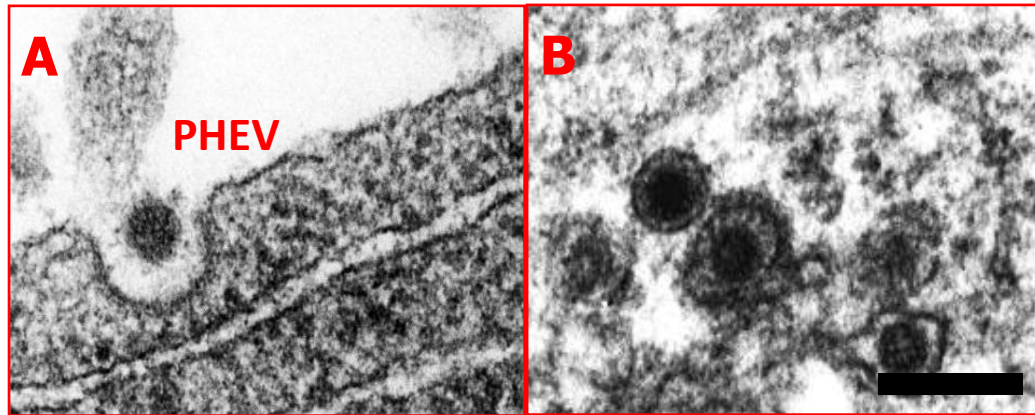
绿：神经元骨架

红：PHEV



N2a细胞感染模型

绿：PHEV



免疫荧光&透射电镜&免疫组化

## 案例四

2010–2019年，吉林松原、农安等主要养羊地区羊群出现“口疮”疫情，尤其春秋季节高发，且羔羊的发病率较高，严重时呈全群发病。



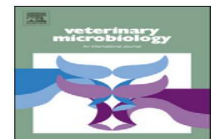
Veterinary Microbiology 142 (2010) 408–415



Contents lists available at ScienceDirect

Veterinary Microbiology

journal homepage: [www.elsevier.com/locate/vetmic](http://www.elsevier.com/locate/vetmic)



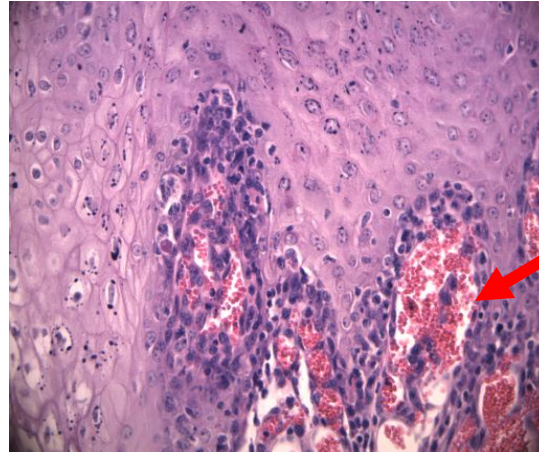
Short communication

Identification and phylogenetic analysis of an Orf virus isolated from an outbreak in sheep in the Jilin province of China

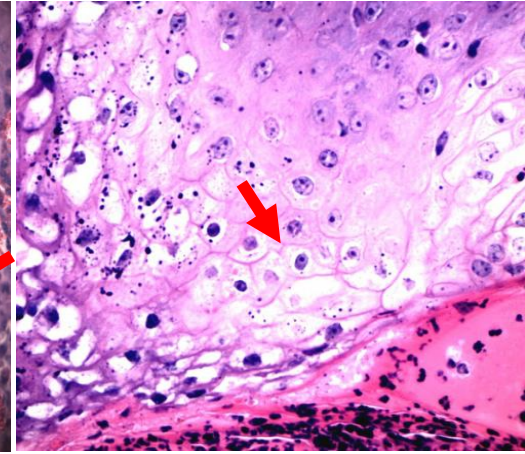
Kui Zhao <sup>a,1</sup>, Deguang Song <sup>a,1</sup>, Wenqi He <sup>a,\*</sup>, Huijun Lu <sup>b</sup>, Bingbing Zhang <sup>a</sup>, Chao Li <sup>c</sup>, Keyan Chen <sup>a</sup>, Feng Gao <sup>a,\*\*</sup>



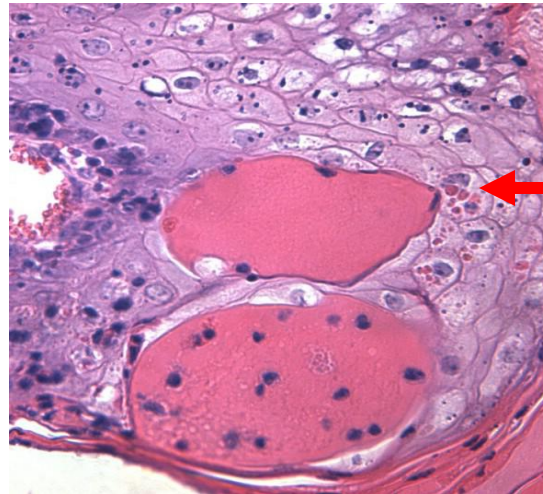
# 羊传染性脓疱病病理变化



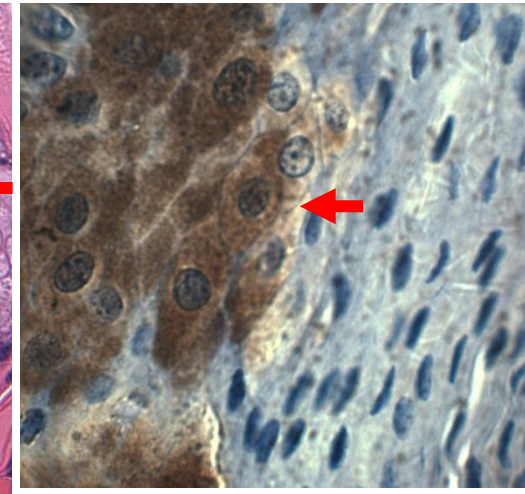
皮肤表皮血管扩张、充血，棘细胞层增厚(H.E. ×40)



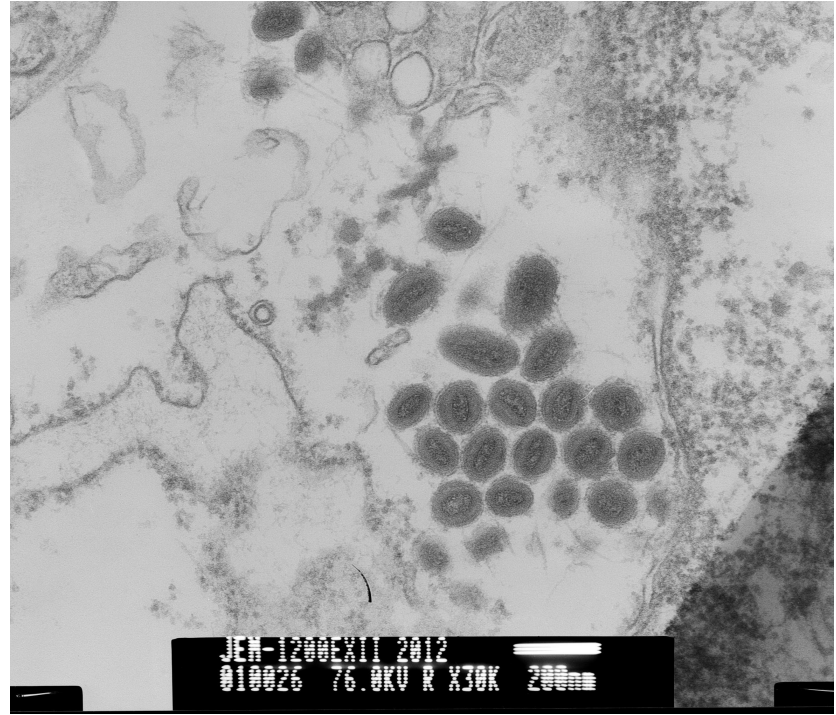
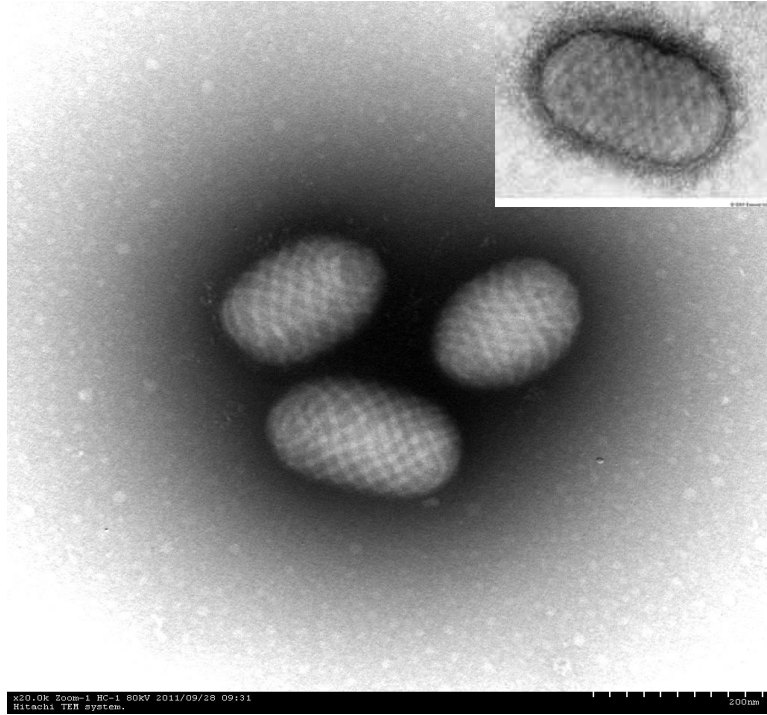
棘细胞水疱变性、网状变性、甚至发生气球样变(H.E. ×40)



嗜酸性病毒包涵体(H.E. ×40)



IHC检测



透射电镜观察



# 案例五

专论综述

中国动物检疫

## 牛结节性皮肤病预警信息与风险管理

孙映雪<sup>1</sup>, Tsviatko Alexandrov<sup>2</sup>, 宋建德<sup>1</sup>, 郑雪光<sup>1</sup>, 魏荣<sup>1</sup>, 陈继明<sup>1</sup>

(1. 中国动物卫生与流行病学中心, 山东青岛 266032;

2. Animal Health and Welfare Directorate, Bulgarian Food Safety Agency, Sofia, Bulgaria)

**摘要:**近年来牛结节性皮肤病 (LSD) 已扩散至俄罗斯和哈萨克斯坦, 有可能在数月或数年内传入中国, 而对中国牛群带来严重威胁。本文阐述了 LSD 在全球扩散情况、预警信息、流行特征、诊断方法, 以及相应的风险管理措施。分析了保加利亚 LSD 防控经验, 包括: 政府和科学界高度重视, 基于传播风险调整防控措施, 抓好感染牛群的快速扑杀和无害化处理, 大规模开展疫苗免疫, 限制活牛运输等。

**关键词:**牛结节性皮肤病; 预警; 风险管理; 防控经验

中图分类号: S851.33 文献标识码: A 文章编号: 1005-944X (2019) 04-0044-05

DOI: 10.3969/j.issn.1005-944X.2019.04.012

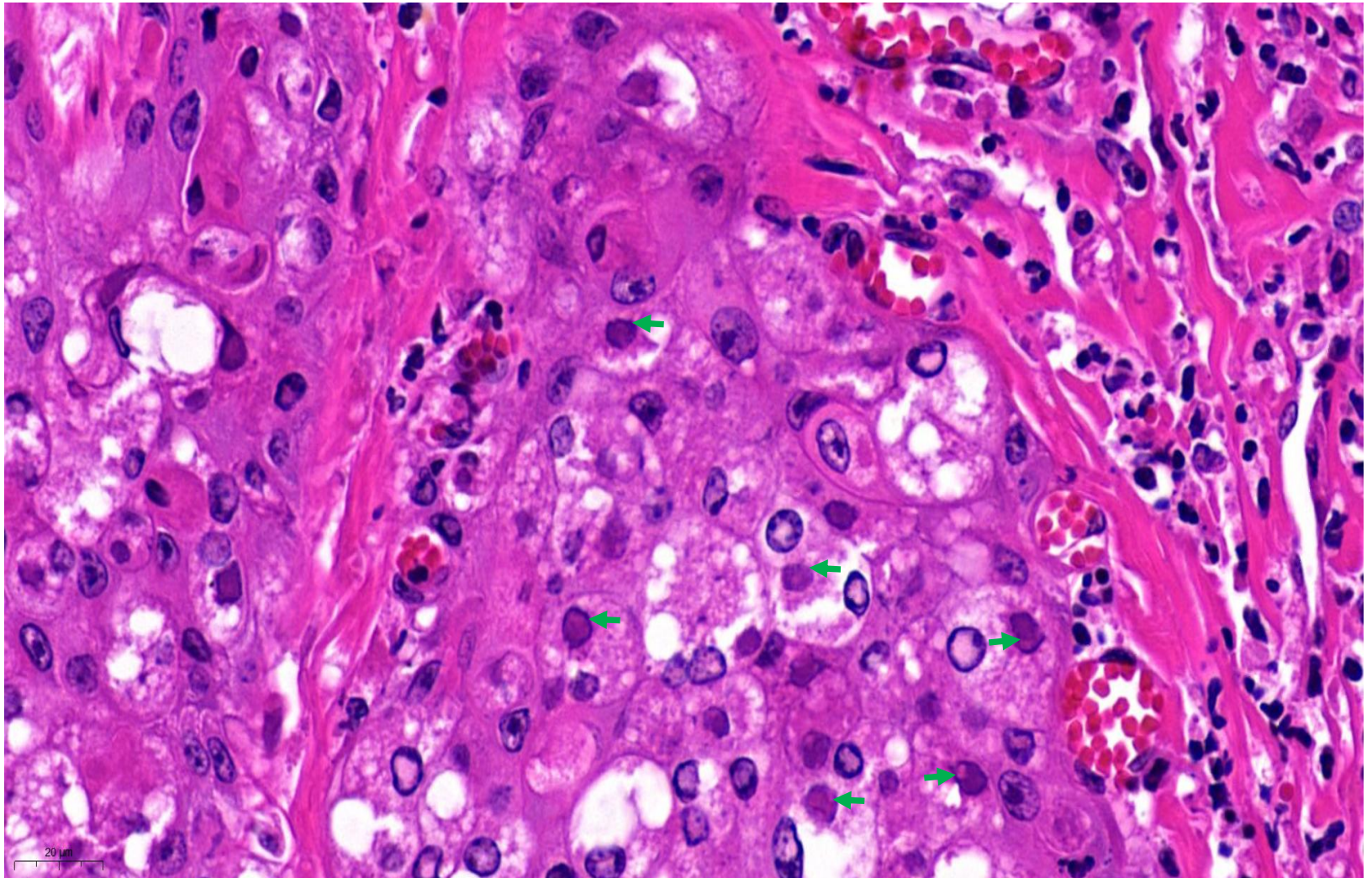


- 1926年在津巴布韦被首次确诊。
- 2015年希腊、俄罗斯、哈萨克斯坦等周边国家频发。
- 2019年8月12日, 首次在我国新疆伊犁州被确诊。
- 2020年6月初, 福建省龙岩市长汀县、江西省瑞金市先后报告发生LSD, 之后广东、安徽、浙江……等9省区均有发生。
- 目前广泛分布于非洲、中东、中亚、东欧等地区。
- 中国农业农村部暂将其按二类动物疫病管理并采取相应防控措施。



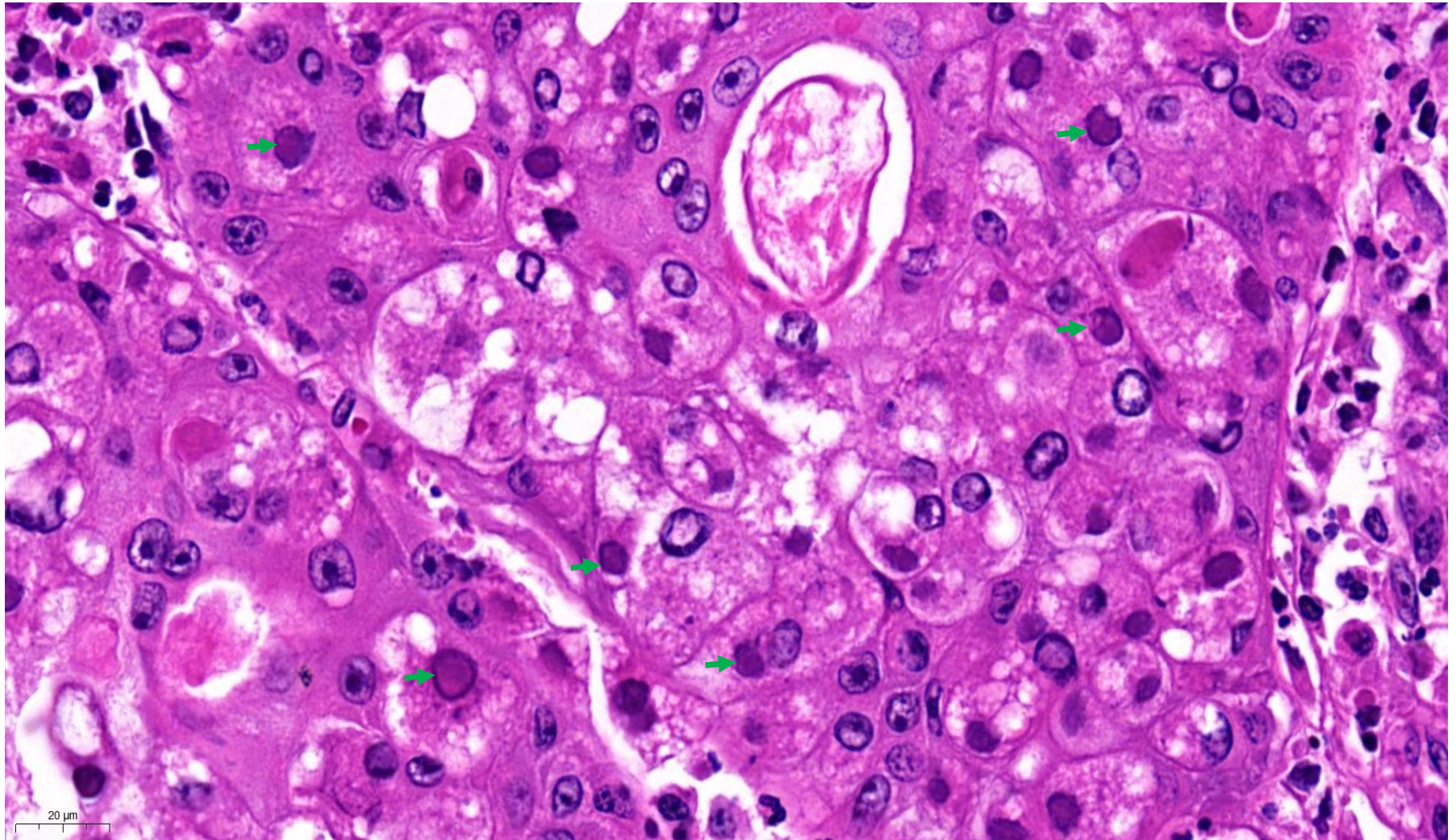
2020年6月以来，我国福建、江西、广东、安徽、浙江.....  
等多个省份已有该病的发生





皮肤棘细胞胞浆内可见病毒包涵体（H.E. ×135）





皮肤棘细胞胞浆内可见病毒包涵体 (H.E. ×135)