Virology 390 (2009) 1–12

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

Pathological manifestations of feline immunodeficiency virus (FIV) infection in wild African lions

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ARTICLE INFO

Article history:
Received 30 December 2008
Returned to author for revision
17 February 2009
Accepted 8 April 2009
Available online 22 May 2009

Keywords:
FIV
Lentivirus
Lions
Wild
Free-ranging
Pathology
Immune depletion

ABSTRACT

Feline immunodeficiency virus (FIV) causes AIDS in the domestic cat (*Felis catus*) but has not been explicitly associated with AIDS pathology in any of the eight free-ranging species of Felidae that are endemic with circulating FIV strains. African lion (*Panthera leo*) populations are infected with lion-specific FIV strains (FIVple), yet there remains uncertainty about the degree to which FIV infection impacts their health. Reported CD4+ T-lymphocyte depletion in FIVple-infected lions and anecdotal reports of lion morbidity associated with FIV seroprevalence emphasize the concern as to whether FIVple is innocuous or pathogenic. Here we monitored clinical, biochemical, histological and serological parameters among FIVple-positive ($N=47$) as compared to FIVple-negative ($N=17$) lions anesthetized and sampled on multiple occasions between 1999 and 2006 in Botswana. Relative to uninfected lions, FIVple-infected lions displayed a significant elevation in the prevalence of AIDS-defining conditions: lymphadenopathy, gingivitis, tongue papillomas, dehydration, and poor coat condition, as well as displaying abnormal red blood cell parameters, depressed serum albumin, and elevated liver enzymes and gamma globulin. Spleen and lymph node biopsies from free-ranging FIVple-infected lions ($N=9$) revealed evidence of lymphoid depletion, the hallmark pathology documented in immunodeficiency virus infections of humans (HIV-1), macaques, and domestic cats. We conclude that over time FIVple infections in free-ranging lions can lead to adverse clinical, immunological, and pathological outcomes in some individuals that parallel sequelae caused by lentivirus infection in humans (HIV), Asian macaques (SIV) and domestic cats (FIVfca).

Introduction

Pathological conditions associated with lentivirus infection in human and animal models include immune depletion, oral lesions caused by opportunistic infections, wasting, renal disease, and frequently a chronic inflammatory response. These conditions have been described as shared disease sequelae in humans infected with HIV, in macaques with SIV or chimeric S/HIV, and in domestic cats with FIV (Table 1). AIDS-defining conditions in HIV and SIV include immunodeficiency indicators such as CD4+ depletion (Freeman et al., 2004; Pandrea et al., 2007; Varbanov et al., 2006), lymphadenopathy (McClure et al., 1989; Quijano et al., 1997; Wang et al., 2003; Yanai et al., 2006), and progressive changes in histopathology consisting of lymphoid hyperplasia, involution, and atrophy (McClure et al., 1989; Quijano et al., 1997; Wang et al., 2003). In humans, loss of condition, or cachexia, is also AIDS-defining (Eid and Orenstein, 2006; Faintuch et al., 2006; Freeman et al., 2004; Kotler et al., 1984). Oral lesions such as gingivitis and papillomavirus associated warts (papillomas) are common in HIV infection and can be useful diagnostic indicators of HIV status since they parallel decline in CD4+ counts and rising viral load (Greenspan and Greenspan, 1997; Greenspan and Greenspan, 2002; Hodgson et al., 2006; Pantanowitz et al., 2006; Reddy, 2007; Woodman et al., 2007; zur Hausen, 2002). The documentation of

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doi:10.1016/j.virol.2009.04.011

Table 1
Comparative sequelae of HIV, SIV, and FIV.

Medical condition present in:	HIV (refs) human	SIV (refs) macaque	FIV_{FCA} (refs) domestic cat	Lions					
				FIVple-negative		FIVple-positive		Odds ratio	*p*-value
				% Affected[b]	(No. lions)[c,d]	% Affected[b]	(No. lions)[e]		
Immunodeficiency									
CD4 depletion[a]									
Absolute number of CD4+ T-cells/mm^3 in peripheral whole blood ± s.e.	(47)	(15, 33)	(1, 2, 22, 25, 32, 45, 46, 49)	0	(5)	100[f]	(8)	na[g]	0.00015
Oral manifestations									
Gingivitis	(7, 16, 17, 38, 39)	(36)	(3, 25, 35)	40.00	(15)	88.40	(43)	11.40	0.00016
Papillomavirus	(7, 16, 17, 18, 21, 34, 38, 39, 52, 55)	nd[h]	(11, 44)	14.30	(14)	53.19	(47)	6.82	0.01009
Chronic inflammatory response									
Lymphadenopathy	(37, 48)	(29, 54)	(3, 6, 35)	41.67	(12)	76.60	(47)	4.58	0.01900
Hyperglobulinemia (serum globulin ≥2 s.d. above mean)[j]	(7, 8)	(51)	(1, 22, 43)	0	(14)	85.71	(46)	na	$<2\times10^{-9}$
Elevated erythrocyte sedimentation rate (ESR ≥2 s.d. above mean)[j]	(24, 27, 40)	nd	nd	13.33	(15)	64.86	(37)	12.00	0.00076
Dehydration (≥4%)	(41)	(4, 20)	(10)	26.67	(15)	63.04	(46)	4.69	0.01408
Non-specific indicators of Ill-health									
Hair and coat abnormalities	nd	nd	nd	13.30	(15)	52.27	(44)	7.12	0.00840
Hypoalbuminemia (marker for cachexia) (serum albumin ≥2 s.d. below mean)[j]	(5, 14, 42)	nd	nd	0	(14)	46.94	(46)	na	0.00129
Anemia (Hemoglobin and/or PCV ≥2 s.d. below mean)[j]	(30, 42)	(19)	(22, 25, 43)	11.11	(18)	55.77	(52)	10.09	0.00101
Cachexia/unexplained weight loss	(12, 13, 26)	(15)	(3, 23, 25, 28, 53)	nd		Observed in 3 FIV+ populations[k]		na	na
Histopathologic evidence of lymphoid response									
Histopathologic evidence of: lymphoid activation	(37, 48)	(29)	(6, 9)	nd		Yes		na	na
Histopathologic evidence of: lymphoid atrophy and depletion	(37, 48)	(29)	(6, 9)	nd		Yes		na	na

[a] Detailed data for CD4 depletion in wild lions is presented in Roelke et al. (2006). Other FIV entries are in this report.

References used in table

1. Ackley et al. (1990); 2. Barlough et al. (1991); 3. Bendinelli et al. (1995); 4. Board et al. (2003); 5. Bonarek et al. (2001); 6. Brown et al. (1991); 7. Coogan et al. (2005); 8. De Milito et al. (2004); 9. Diehl et al. (1995); 10. Egberink et al. (1990); 11. Egberink et al. (1992); 12. Eid and Orenstein (2006); 13. Faintuch et al. (2006); 14. Feldman et al. (2000); 15. Freeman et al. (2004); 16. Greenspan and Greenspan (1997); 17. Greenspan and Greenspan (2002); 18. Hawes et al. (2003); 19. Hillyer et al. (1993); 20. Hodge et al. (1998); 21. Hodgson et al. (2006); 22. Hofmann-Lehmann et al. (1997); 23. Hutson et al. (1991); 24. Kim et al. (2006); 25. Kohmoto et al. (1998); 26. Kotler et al. (1984); 27. Lifson et al. (1995); 28. Matsumura et al. (1993); 29. McClure et al. (1989); 30. Mocroft et al. (1999); 31. Nagase et al. (2001); 32. Novotney et al. (1990); 33. Pandrea et al. (2007); 34. Pantanowitz et al. (2006); 35. Pedersen et al. (1987); 36. Prospero-Garcia et al. (1996); 37. Quijano et al. (1997); 38. Reddy (2007); 39. Reznik (2005); 40. Schwartlander et al. (1993); 41. Selwyn and Rivard (2003); 42. Shah et al. (2007); 43. Sparkes et al. (1993); 44. Sundberg et al. (2000); 45. Tompkins et al. (1991); 46. Torten et al. (1991); 47. Varbanov et al. (2006); 48. Wang et al. (2003); 49. Willett et al. (1993); 50. Willett et al. (1997); 51. Wong et al. (1999); 52. Woodman et al. (2007); 53. Yamamoto et al. (1989); 54. Yanai et al. (2006); 55. zur Hausen (2002).

[b] Medical condition for each lion was scored as "affected" if the individual was ever found to be abnormal (on physical exam) or have a blood value 2 standard deviations or more away from the mean of the FIV-negative lions (toward a less fit value).

[c] Number of individual lions examined (for each parameter only a single observation date was used per lion).

[d] FIV-negative lions = 23 lions (27 observation dates evaluated).

[e] FIV-positive lions = 54 lions (84 observation dates evaluated).

[f] Two standard deviations below the mean for the FIV-negative lions is 810 CD4+ cells.

[g] na — not applicable.

[h] nd — not documented.

[j] Mean ± 2 s.d. for FIV-negative lion values are:

Globulin (measured and/or calculated)	
Measured	4.44 ± 0.90 g/dL
T. protein minus albumin	3.99 ± 0.72 g/dL
ESR (EDTA whole blood)	10.5 ± 28.0 mm/h
ESR (heparin whole blood) used both sample types to determine abnormal values	23.9 ± 37.3 mm/h
Albumin	3.7 ± 0.76 g/dL
Hemoglobin	12.26 ± 0.90 g/dL
Packed cell volume (PCV)	40.0 ± 7.0%

[k] Serengeti National Park (MER), Okavango Delta (P. Kat, personal communication), Krugar National Park (Ide 2002).