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ORIGINAL ARTICLE

Evaluation of the presence and distribution of leptomeningeal inflammation in SIDS/SUDI cases and comparison with a hospital-based cohort

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Abstract

Introduction Prior research demonstrates that leptomeninges of infants and late-term fetuses derived from a non-traumatic, hospital-based cohort contain a surprisingly large number of inflammatory cells and stainable iron. These were present irrespective of the findings from the general autopsy, the neuropathologic examination, and the mode of delivery.

Materials and methods We applied a similar methodology to a sudden infant death syndrome/sudden unexpected death in infancy (SIDS/SUDI) cohort. Forty-two SIDS/SUDI cases autopsied between 2006 and 2014 by the San Diego County Medical Examiner's Office were identified. An interpretable amount of leptomeninges from at least two areas of the brain (cerebral cortex, brain stem, cerebellum) were present in each case. Immunoperoxidase (IPOX) staining with CD45 and CD68 was performed and Perl's method was used to detect the presence of iron. The number of immunoreactive cells per IPOX stain within the leptomeninges in each slide was manually tabulated and the density subsequently quantified. The presence or absence of stainable iron was noted.

Results This cohort represented 22 males and 20 females ranging in age from 2 to 311 days, with relatively evenly divided modes of delivery. The examined brain sections included 32 of the cerebral cortex, 18 of the brain stem, and 36 of the cerebellum. The lengths of the examined leptomeninges ranged from 2 to 40 mm. The ranges of the number of cells per millimeter, and the standard deviations of the means were wide and varied. Overall, there was no significant difference in the number of CD45 or CD68 immunoreactive cells/millimeter between the three brain sites. Comparing this cohort to a subpopulation of hospitalized infants in our prior study, there were no significant differences between the density of inflammatory cells in the sections from the cerebral cortex and brain stem. There were differences in the CD68 densities, particularly in the cerebellar sections which may be attributable to methodological differences. Iron was identified in only a single section in this cohort but was present in most of the cases in the hospital-based cohort.

Conclusion This study further elucidates the relevance of the presence of inflammatory cells and iron in the leptomeninges. Whether in a hospital-based or more forensically relevant population, the presence of inflammatory cells in the leptomeninges (even in great abundance) is common.

Keywords SIDS/SUDI · Infant leptomeninges · Forensic science

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Introduction and objectives

The leptomeninges are composed of the pia and arachnoid mater connected by strands known as the arachnoid trabeculae [1, 2]. They are now known to be involved in various physiologic and pathologic roles. Physiologically, leptomeningeal cells may release growth factors important for neuronal and glial cell survival, and pathologically, they may promote cytokine release in the presence of systemic inflammatory conditions [3]. In our previous study, we described the presence of inflammatory cells in 33 cases involving hospital-based autopsies of fetuses and infants,

challenging the traditional belief that under normal conditions, the leptomeninges should be devoid of inflammatory cells [4].

Our goal in the current study was to determine the presence and pattern of inflammatory cell distribution and iron deposition in a more forensically relevant population of deaths certified as sudden infant death syndrome/sudden unexpected death in infancy (SIDS/SUDI). SIDS/SUDI is a label covering a challenging group of infant deaths whereby after a thorough postmortem examination, death scene investigation, and review of the clinical history, the death of the infant remains unexplained [5]. It is most common in infants less than 1 year of age and currently a leading cause of infant mortality in the USA [6]. The presence of inflammatory cells in the leptomeninges could be interpreted to reflect an active inflammatory process [7] while the presence of iron deposition would signify a prior episode of bleeding [8]. Either of these findings could potentially influence the certification of the cause of death. The presence of either inflammation or iron deposition in the leptomeninges in SIDS/SUDI cases has not been previously investigated. Having studied a hospital-based cohort [4] previously, we were interested in comparing those results of the distribution of inflammatory cells and iron deposition to a more forensically relevant population.

Materials and methods

Subject selection

A total of 42 SIDS/SUDI cases between 2006 and 2014 in which full neuropathologic examinations had been performed at the San Diego County Medical Examiner's Office were identified. Each of these cases had at least two microscopic sections of brain of interest (cerebral cortex, brain stem, and cerebellum). Each slide was microscopically screened by one of the authors (TLH) to ensure that at least 2 mm of leptomeninges from each section was included.

For the purposes of this study, the "hospital cohort" refers to a subpopulation (group 1) of cases from our previous study [4]. "Group 1" (hereafter referred to as "hospital cohort") was selected as a basis for comparison because of the similarity in age ranges (infants with a gestational age above 33 days of age) with the SIDS/SUDI cohort. "Group 2" of the previous hospital cohort was not included for comparison as it was composed of a younger population (up to 33 postnatal days). The hospital cohort was compared with 36 age-matched cases from the SIDS/SUDI group.

Sample fixing, staining and immunohistochemistry

Slides of routinely processed formalin-fixed, paraffin-embedded sections were prepared and stained with antibodies to CD45 (dilution 1:100) and CD68 (dilution 1:100). CD45, also known as leucocyte common antigen, is uniquely expressed on the surface of all leucocytes and their progenitor cells including neutrophils, eosinophils, basophils, lymphocytes, and monocytes [9]. CD68 is expressed on monocytes and macrophages [10]. Immunoperoxidase (IPOX) staining was performed, following microwave antigen retrieval in citrate buffer at pH 6, on an automatic stainer [11]. The Perl's staining method was utilized to detect iron deposition [12].

Examination of samples

At a magnification of × 400, the number of immunoreactive cells and iron-containing cells was quantified by one author (EJ) to reduce inter-observer bias. The accuracy was cross-checked by a second observer (TLH). In this cohort, all leptomeninges available within each slide were analyzed. For cerebellar sections, leptomeninges lining the sulci were noted as "sulci" and those lining the tops of the folia as "folia." The length of leptomeninges was measured in millimeters and results reported as immunoreactive cells/millimeter. Iron was recorded as either present or absent.

Analysis of results

The number of immunoreactive cells from each brain site, along with the associated leptomeningeal lengths, was calculated. From this, the mean cellular densities of CD45- and CD68-immunoreactive cells in each case for each site were calculated (Tables 4a–c). Any statistically significant differences between the SIDS/SUDI and hospital cohorts were calculated using R [13]. Since the samples are not normally distributed, we applied the non-parametric Mann-Whitney *U* test. Unlike the *t* test, the *U* test does not make assumptions about normality and is therefore appropriate in this situation.

Results

SIDS/SUDI demographics

In the current study, there were 22 male and 20 female cases. The ages of these cases ranged between 2- and 311-days-old (mean 101.5 days). Thirty-six of the 42 cases were older than 33 days. Thirteen cases were delivered by Cesarean-section, 28 vaginally, and in one case, the mode of delivery was not recorded.

These cases (Table 1) had undergone routine general and neuropathological examinations by the pathologists at the San Diego County Medical Examiner's Office. All of the cases reported no significant findings (e.g., systemic infections, previously unrecognized antemortem disease processes) on general autopsy, except for non-specific postmortem findings such as thymic and pericardial petechiae. Only two cases had significant

Table 1 Demographics of all cases including age, gender, cause and manner of death, and investigative findings. "Investigative findings" represent general, neuropathological and relevant scene and investigative findings. *FT* full-term (40 gestational weeks and above), *CS* Cesarean section, *VD* vaginal delivery, *Unk* unknown, *UD* undetermined, *N* natural, *H/O* history of, *BS SIDS/SUDI* SIDS/SUDI with bed sharing, *BS* bed sharing, *SIDS OM* SIDS with otitis media as a contributing factor, *SIDS LD* SIDS with chronic lung disease of infancy as a contributory factor, *DD* developmental delay, *BC + OM* otitis media with positive blood culture; *SGH* subgaleal hemorrhage, *PFO* patent foramen ovale, *hge* hemorrhage

	Age						
Case	Gestational (weeks)	Post-natal (days)	Gender	Mode of delivery	COD	MOD	Investigative findings
1	39	229	M	CS	UD	UD	Frequent BS
2	FT	194	F	VD	BS SIDS	N	Nil
3	FT	179	M	VD	BS SIDS	UD	H/O BC+ OM
4	FT	30	F	VD	BS SIDS	UD	Nil
5	36	29	M	VD	BS SIDS	UD	Nil
6	36.6	75	M	VD	BS SIDS	UD	Nil
7	FT	177	M	CS	SUDI	UD	Nil
8	FT	105	M	CS	SIDS	N	Nil
9	FT	12	F	VD	SIDS	N	Nil
10	FT	119	M	VD	SIDS	N	H/O pylorostomy
11	Unk	137	F	Unk	SUDI	UD	Minimal SGH
12	FT	48	M	VD	SIDS	N	Frequent BS
13	38	44	M	VD	SIDS	N	Nil
14	39	52	M	VD	BS SIDS	N	Nil
15	FT	27	F	VD	SIDS	N	H/O "stuffy nose"
16	39	40	M	VD	BS SIDS	UD	Nil
17	39	52	M	VD	BS SIDS	UD	H/O "cough"
18	36	101	F	VD	BS SIDS	UD	H/O OM DD
19	39	120	F	VD	BS SIDS	UD	H/O OM
20	34	211	F	VD	SIDS	N	H/O OM
21	39	50	F	CS	SIDS OM	UD	H/O OM
22	FT	29	M	VD	BS SIDS	N	Nil
23	FT	68	F	CS	BS SIDS	N	Small for age
24	FT	124	F	VD	SIDS	N	Nil
25	FT	74	F	VD	SIDS	N	Nil
26	FT	101	F	VD	SUDI	UD	Nil
27	FT	104	M	CS	SIDS OM	N	Nil
28	FT	75	F	CS	SIDS	N	Frequent BS
29	FT	93	M	VD	SIDS	N	Hepatic steatosis, "cough"
30	36	311	F	VD	SIDS	N	Polymicrogyria, micrencephaly
31	27	119	F	CS	SIDS LD	N	Old cerebellar hem, PDA ligation
32	Unk	110	M	CS	SIDS LD	N	Small for age
33	FT	47	F	VD	BS SUDI	UD	Nil
34	FT	40	M	CS	BS SUDI	UD	Nil
35	FT	2	M	CS	SUDI	N	Hepatic steatosis
36	35	240	M	VD	SIDS	N	Nil
37	FT	196	M	VD	SIDS	N	Nil
38	FT	118	F	CS	SIDS	N	Frequent BS
39	FT	124	M	VD	SIDS	N	PFO, frequent BS
40	FT	94	F	VD	SIDS	N	Nil
41	FT	56	M	VD	SIDS	N	Nil
42	27	81	F	CS	BS SIDS	UD	Nil

neuropathology findings—one case with prior cerebellar hemorrhage and one with polygyria and micrencephaly. These neuropathologic findings were not considered to have been contributory causes of death in these infants.

With regard to the cause of death, 26 cases (62%) were classified as SIDS/SUDI with contributing factors of otitis media (two cases), chronic lung disease (two cases), and cerebellar malformations (one case). The second most common cause of death was SIDS with bed sharing (15 cases, 36%). One case (2%) reported an undetermined cause of death (though with no investigative or anatomic findings differing from the SIDS/SUDI-classified cases). There were 26 cases (62%) in our study whose manners of death were determined to be "natural"—22 of these were classified as SIDS/SUDI and four SIDS with bed sharing. Of these natural deaths, two cases had some form of chronic lung disease of prematurity and one case each had otitis media or cerebral malformation. Sixteen cases (38%) were assigned an undetermined manner of death (allowing for the possibility of accidental asphyxia while bed sharing). The causes of death of 11 of these were classified as SIDS with bed sharing, four case (25%) as SIDS/SUDI, and one case as undetermined. One SIDS case assigned an undetermined manner of death had otitis media.

Thirty-two cerebral cortical sections, 16 brain stem sections, and 36 cerebellar sections were studied. The lengths of leptomeninges (Table 2) ranged between 2 and 34 mm in the cortical sections, and between 5 and 30 mm in the brain stem sections. With regard to the cerebellar sections, 30 of the 36 sections had between 5 and 30 mm of leptomeninges dipping into the sulci, and six cases had between 2 and 40 mm only overlying the folia.

Density of inflammatory cells in SIDS/SUDI leptomeninges

The mean number of immunoreactive cells/millimeter for CD45 and CD68 from the cortical sections was 7.5 cells/mm and 22.1 cells/mm, respectively. The brain stem sections had a mean of 10.8 immunoreactive cells/mm for CD45 and 16.7 cells/mm for CD68. Overall, the cerebellar sections had 9.9 CD45-immunoreactive cells/mm and 27.5 CD68-immunoreactive cells/mm (Table 3). The ranges of the number of cells per millimeter and standard deviations of the means were wide and varied; in some instances, the standard deviations were greater than the mean.

Table 3 Mean immunoreactive cells/millimeter in the cerebral cortex, brain stem, and cerebellum

	CD45		CD68	
	Range	Mean ± SD	Range	Mean ± SD
Cerebral cortex	1.1–29.7	7.5 ± 7.4	6.3–68.4	22.1 ± 14.8
Brain stem	0.8–53.5	10.8 ± 11.3	6.8–59.0	16.7 ± 11.8
Cerebellum	3.5–22.3	9.9 ± 4.4	7.0–89.2	27.5 ± 15.7

Comparisons between SIDS/SUDI and hospital cohort

There were 36 SIDS/SUDI cases which involved infants greater than 32 days of age, allowing for age-matched comparisons with our previous hospital-based cohort. The total length of leptomeninges sampled in the SIDS/SUDI and the hospital cohort according to brain site is shown in Table 2. The counts of immunoreactive cells in the sulci of the cerebellar sections in the hospital cohort were not performed. In the hospital cohort, leptomeninges covering the folia were abundant which was not the case in the SIDS/SUDI cohort.

The results of the comparison of cell counts/millimeter by stain and anatomic site in the SIDS/SUDI and hospital cohorts are shown in Table 4. There was a mean of 8.3 ± 7.6 CD45-immunoreactive cells/mm in the SIDS/SUDI cortical sections, and 21.0 ± 22.3 cells/mm in the hospital group ($p = 0.01$). In the same section, there was a mean of 23.3 ± 15.2 CD68-immunoreactive cells/mm in the SIDS/SUDI cohort and 28.0 ± 18.7 cells/mm in the hospital group (p = NS). For the brain stem sections, there were 5.3 ± 9.6 CD45-immunoreactive cells/mm in the SIDS/SUDI group and 11.9 ± 9.5 cell/mm in the hospital cohort ($p = 0.02$). There were 8.0 ± 11.9 CD68-immunoreactive cells/mm in the SIDS/SUDI group and 11.3 ± 84.8 cells/mm in the hospital group (p = NS). In the cerebellar sections, there were 9.8 ± 4.4 CD45-immunoreactive cells/mm in the SIDS/SUDI group and 10.9 ± 8.2 cells/mm in the hospital cohort (p = NS). In the SIDS/SUDI and hospital groups, there were 27.8 ± 15.6 and 12.6 ± 13.4 CD68-immunoreactive cells/mm, respectively ($p = 0.002$). These numbers reflect both folia and sulci cell

Table 2 Total length of leptomeninges per brain site, with mean and standard deviation of SIDS/SUDI and hospital cohorts

		Cerebral cortex	Brain stem	Cerebellum sulci	Cerebellum folia
Hospital cohort (mm)	Total	699	1065		581
	Mean ± SD (range)	18.8 ± 10.5 (5–41)	28.7 ± 17.0 (10–83)		20.3 ± 11.1 (10–47)
SIDS/SUDI (mm)	Total	566	282	549	119
	Mean ± SD (range)	17.7 ± 9.6 (2–34)	15.7 ± 6.5 (5–30)	18.3 ± 7.0 (5–30)	19.8 ± 5.1 (2–40)

Table 4 Cells counts per millimeter of leptomeninges for each brain area sampled in SIDS/SUDI and hospital cohorts and comparison for statistical significance

	Stain	SIDS/SUDI Mean ± SD ($n = 36$)	Hospital Mean ± SD ($n = 16$)	p value
Cerebellum	CD45	9.8 ± 4.4	10.9 ± 8.2	NS
	CD68	27.8 ± 15.6	12.6 ± 13.4	0.002
Brain stem	CD45	5.3 ± 9.6	11.9 ± 9.5	0.02
	CD68	8.0 ± 11.9	11.3 ± 84.8	NS
Cortex	CD45	8.3 ± 7.6	21.0 ± 22.3	0.01
	CD68	23.3 ± 15.2	28.0 ± 18.7	NS
Total average	CD45	11.8 ± 11	14.2 ± 10.7	0.013
	CD68	29.7 ± 31.9	16.9 ± 10.5	0.013

counts from the SIDS/SUDI group whereas in the hospital group, only counts from the leptomeninges covering the gyri of the cerebral cortex and the folia of the cerebellar sections were included.

Overall (including cerebellar folia and sulci counts), the mean density of CD45-immunoreactive cells/mm in the SIDS/SUDI cohort was 11.8, whereas within the hospital group, it was 14.2 ($p = 0.013$). The mean density of CD68-immunoreactive cells/mm in the SIDS/SUDI cohort was 29.7 and in the hospital group, 16.9 ($p = 0.013$). When cerebellar cases including only folia counts were considered, the total average CD45- and CD68-immunoreactive cell densities were 10.4 cells/mm and 24.5 cells/mm, respectively ($p = 0.02$ compared with corresponding hospital cohort).

On close inspection, there were five cases in which there were leptomeninges only over the folia (folia counts) (Table 5) and 26 cases in which analyzed leptomeninges also included the sulci (Table 6). In the folia group, there were 12.2 ± 7.6 and 10.9 ± 8.2 CD45-immunoreactive cells/mm (p = NS) in the SIDS/SUDI and hospital-based groups, respectively. In the folia subset of the SIDS/SUDI cohort and the hospital cohort, there were 21.6 ± 8.6 and 12.6 ± 13.4 CD68-immunoreactive cells/mm, respectively (p = NS). Within the sulci group (Table 6; incorporating counts in all areas of the leptomeninges), there were 9.4 ± 3.5 and 10.9 ± 8.2 CD45-immunoreactive cells/mm in the SIDS/SUDI and hospital groups, respectively (p = NS). There were 29.0 ± 16.5 CD68-immunoreactive cells/mm in the SIDS/SUDI cohort, versus 12.6 ± 13.4 cells/mm in the hospital group ($p = 0.001$).

Table 5 Comparison of cell counts/millimeter of leptomeninges in cerebellar sections in SIDS/SUDI (including only folia counts) and hospital cohort. The total averages reflect the cell counts/millimeter of all of the brain sections for the SIDS/SUDI subgroup and all of the hospital cohort

	Stain	SIDS/SUDI Mean ± SD ($n = 5$)	Hospital Mean ± SD ($n = 16$)	p value
Cerebellum	CD45	12.2 ± 7.6	10.9 ± 8.2	NS
	CD68	21.6 ± 8.6	12.6 ± 13.4	NS
Total average	CD45	13.3 ± 4	14.2 ± 10.7	NS
	CD68	29.4 ± 3.8	16.9 ± 10.5	NS

Iron deposition

In contrast to our hospital cohort study in which stainable iron was found in most cases irrespective of the mode of delivery, only one case in the SIDS/SUDI cohort demonstrated stainable iron in the cerebellum section (Fig 1). The iron deposition was grossly evident in this case, as reported in the neuropathological examination.

Discussion

There was a notable difference in the methodology employed in our previous study compared with this study: all of the cases in the hospital-based cohort had been reviewed and neuropathologic diagnoses rendered by the same neuropathologist (TLH). The cases in the present study involved different pathologists, thus potentially representing a heterogeneous set of skills in tissue sampling and diagnostic ability. The likely consequences of a larger number of involved pathologists included a wide range of available tissue samples for each case, and a paucity of leptomeninges available for study. We attempted to overcome the second limitation by including the entirety of the leptomeninges on each slide, unlike in our previous study, wherein only leptomeninges covering the gyri of the cerebral cortex and folia of cerebellar sections were assessed.

Inflammatory cells were present in the leptomeninges in all of the slides in all of the cases, which was concordant with our prior observations that the leptomeninges contain a surprisingly large number of inflammatory cells. The number of

Table 6 Comparison of cell counts/millimeter of leptomeninges in cerebellar sections in SIDS/SUDI (including cases in which counts of both folia and sulci were performed) and hospital cohort. The total averages reflect the cell counts/millimeter of all of the brain sections for the SIDS/SUDI subgroup and all of the hospital cohort

	Stain	SIDS/SUDI Mean ± SD ($n = 26$)	Hospital Mean ± SD ($n = 16$)	p value
Cerebellum	CD45	9.4 ± 3.5	10.9 ± 8.2	NS
	CD68	29.0 ± 16.5	12.6 ± 13.4	0.001
Total average	CD45	10.5 ± 6.8	14.2 ± 10.7	NS
	CD68	23.8 ± 9.2	16.9 ± 10.5	0.00001

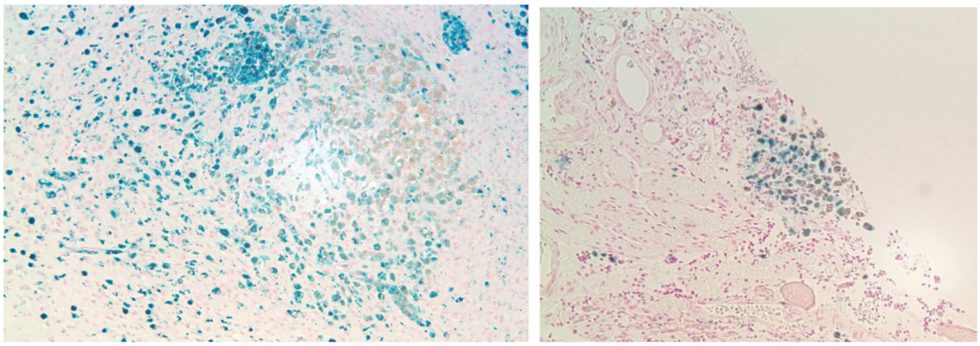

Fig. 1 Presence of stainable iron in a single case involving the cerebellum of an infant with a history of marked prematurity, lung disease, and prior surgical procedure (× 100)

inflammatory cells in cases with no neuropathologic findings was not significantly lower than that with reported pathologies, when compared with the age-matched hospital cohort. The significant number of inflammatory cells is at odds with the common conception that the presence of inflammatory cells equates to significant pathology or a traumatic event [14]. However, eight cases in our SIDS/SUDI cohort had reported signs of possible infection (otitis media, "cough," "stuffy nose") in the weeks preceding death and in two cases, the presence of otitis media was considered a significant contributory condition in death. While one might postulate that the presence of inflammatory cells in the leptomeninges in the otitis media cases could represent an extension of the inner ear process or an over-active response of an immature immune system at work, it is noteworthy that the cell counts/millimeter in the leptomeninges were not significantly different between the otitis cases and the remainder of the cohort [15, 16].

The "triple risk model" [14] posits that SIDS/SUDI is a consequence of the interplay between the infant's intrinsic vulnerability, a critical developmental period, and extrinsic factors in the infant's environment. Progression of basic science SIDS/SUDI research will hopefully uncover more underlying biological causes and intrinsic factors rather than the currently accepted absence of pathologic findings [17, 18]. Preferences in nomenclature [19, 20] by different examining pathologists were noted in this study whereby cases with SIDS/SUDI with bed sharing causes were mannered as both "natural" and "undetermined."

Only one slide in one case demonstrated the presence of stainable iron. This is in contrast to our previous hospital cohort where stainable iron was identified in the majority of cases, irrespective of the mode of delivery. With regard to the singular slide with iron deposition in this study, it is noteworthy that the pathologist recognized it as a remote process that played no role in death of this infant. To account for the difference in the plentifulness of iron deposition in these two cohorts, it is important to recognize that many of the infants (10 of 16) in the hospital cohort had disease processes which would have predisposed them to cerebral hemorrhages or infarctions (e.g., congenital heart disease) or hypoxic/ischemic encephalopathy (with ischemia-related hemorrhages).

Conclusion

We confirmed, in part, our previous study that the leptomeninges of infant brains contain an unexpectedly abundant number of inflammatory cells. Given the multitude of various disease processes found in our prior hospital-based study, the presence of inflammation may not have been surprising. However, in the current, more forensically relevant cohort of SIDS/SUDI cases where active disease processes and infections were the exception, the degree of leptomeningeal inflammation is more surprising. Accordingly, when a pathologist is endeavoring to arrive at a cause of death in an otherwise negative death investigation, the presence of some degree of inflammatory infiltrate in the leptomeninges should not be considered a priori evidence of a potentially life-threatening process. The presence of leptomeningeal inflammatory cells must be viewed holistically and in context with the most recent developments in the research in the field.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest for this study.

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